An Imaging Approach to Persistent Neonatal Jaundice

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Fifteen patients with persistent neonatal jaundice were evaluated by sonography and radionuclide scintigraphy. The sonographic features of both neonatal hepatitis and biliary atresia are nonspecific. Hepatobiliary scintigraphy after phenobarbital pretreatment in patients with neonatal hepatitis demonstrates normal hepatic extraction and delayed tracer excretion into the gastrointestinal tract. If there is neonatal hepatitis with severe hepatocellular damage, the hepatic extraction of tracer activity is decreased and excretion may be delayed or absent. Patients under 3 months of age with biliary atresia have normal hepatic extraction of tracer with no excretion into the gastrointestinal tract. Sonography in patients with a choledochal cyst shows a cystic mass in the porta hepatis with associated bile-duct dilatation. Hepatobiliary scintigraphy confirms that the choledochal cyst communicates with the biliary system. Initial sonography demonstrates hepatobiliary anatomy; subsequent phenobarbital-enhanced radionuclide scintigraphy determines hepatobiliary function. An expedient diagnostic approach is recommended for the evaluation of persistent neonatal jaundice.

The most common causes of conjugated hyperbilirubinemia in neonates are neonatal hepatitis and biliary atresia. Choledochal cyst is a less common biliary-tract abnormality that may or may not be associated with biliary atresia in the neonate. Conventional laboratory tests fail to differentiate among neonatal hepatitis, biliary atresia, and choledochal cyst.

The Kasai procedure of hepatic portoenterostomy for biliary atresia is most successful when performed early in life: 91% of patients operated on before age 60 days will have sustained bile drainage; 56% of patients drain bile if surgery is performed between 61 and 70 days of age; 43% of infants have sustained bile drainage if surgery takes place between the ages of 71 and 90 days; and only 17% have successful bile drainage if operated on beyond age 3 months [1]. Therefore, it is critical to determine accurately the cause of persistent neonatal jaundice as soon as possible in order to select appropriate therapy.

We recently evaluated 15 infants with persistent neonatal jaundice by sonography and radionuclide scintigraphy. Final diagnoses included biliary atresia (seven), neonatal hepatitis (seven), and choledochal cyst (one). The sonographic findings and hepatobiliary scintigraphic patterns of these 15 patients are presented. A diagnostic approach, including sonography for anatomy and hepatobiliary scintigraphy for function, is recommended for the evaluation of persistent neonatal jaundice.

Subjects and Methods

Fifteen consecutive jaundiced infants with conjugated hyperbilirubinemia since the neonatal period (first month of life) were studied prospectively with hepatobiliary sonography and scintigraphy over a 15-month period (February 1982 to April 1983) at Duke University Medical Center. Serum bilirubin levels were obtained on the day before or day after the hepatobiliary scintigraphic examination. The final diagnosis was confirmed independently by operative

Received June 15, 1983; accepted after revision October 11, 1983.

Presented at the annual meeting of the Society for Pediatric Radiology, Atlanta, April 1983.

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AJR 142:461–465, March 1984
0361–803X/84/1423–0461

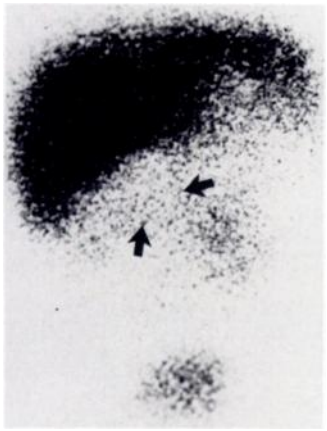

Fig. 1.—Neonatal hepatitis. Sonography showed enlarged gallbladder 3.5 cm in greatest length. Tracer activity in gastrointestinal tract (*arrows*) on ^{99m}Tc-DISIDA image. Normal hepatic extraction of tracer. Some activity within kidneys and bladder.

cholangiography and liver biopsy, autopsy, percutaneous liver biopsy, or clinical course.

Hepatobiliary sonography was performed with a mechanical-sector real-time unit (Advanced Technology Labs.) with a 3.5 or 5.0 MHz transducer. Several patients also had static B-mode sonography with a Picker Echoview 80 L with a 3.5 or 5.0 MHz transducer. Several transverse, longitudinal, and oblique sections were obtained through the liver, gallbladder fossa, and extrahepatic bile ducts. Images were analyzed for liver size, liver echogenicity, intrahepatic bile-duct size, extrahepatic bile-duct size, presence or absence of identifiable gallbladder, size of gallbladder, and presence or absence of cystic mass in the porta hepatis.

Patients were prepared for hepatobiliary scintigraphy by oral administration of phenobarbital in a dose of 5 mg/kg/day in two divided doses for at least 5 days before the examination [2]. Patients were not fed for 1 hr before until 1–2 hr after injection of the radiopharmaceutical. After the intravenous injection of ^{99m}Tc diisopropyl iminodiacetic acid (DISIDA, Disofenin) in a dose of 50 μCi (1.85 MBq)/kg (minimum of 1 mCi [37 MBq]), anterior images of the abdomen were obtained at 5-min intervals up to 1 hr. Subsequently, images were obtained at 2, 4, 6, 8, and occasionally 24 hr after injection. Lateral images were usually obtained at 30 min and 1 hr. Additional lateral or oblique views were obtained if needed to determine the presence of tracer in the gastrointestinal tract [3].

Results

The 15 infants evaluated with sonography and scintigraphy for persistent neonatal jaundice were 10 boys and five girls. The age at diagnosis ranged from 7 days to 2 years. Direct serum bilirubin ranged from 3.7 to 15.7 mg/dl; total serum bilirubin ranged from 4.4 to 34.4 mg/dl. The final diagnoses were biliary atresia (seven patients), neonatal hepatitis (four), severe neonatal hepatitis (three), and choledochal cyst (one). Surgical procedures for biliary atresia included Kasai hepatic portoenterostomy (four), modified Kasai portoenterostomy (two), and a hepatic portocholecystostomy (gallbladder Kasai) procedure (one).

Liver echogenicity was normal in all 15 patients. The liver was enlarged on sonography in two patients with neonatal hepatitis and in two patients with biliary atresia. The intra- and extrahepatic bile ducts were of normal caliber in all patients with neonatal hepatitis and biliary atresia. A gallbladder with greatest length of at least 1.5 cm was considered normal in size; a gallbladder longer than 3 cm was considered enlarged. Two patients with biliary atresia had gallbladders of normal size according to these sonographic criteria. One patient with neonatal hepatitis (fig. 1) and one patient with choledochal cyst had enlarged gallbladders. The patient with a choledochal cyst had a large cystic mass in the porta hepatis that communicated with dilated bile ducts.

All patients with neonatal hepatitis (fig. 1) and all patients with biliary atresia (figs. 2 and 3) under 3 months old had normal hepatic extraction of DISIDA. Three patients with severe neonatal hepatitis (neonatal hepatitis with severe hepatocellular damage) (fig. 4) and two patients with biliary atresia over 3 months old had decreased hepatic extraction of tracer. The excretion of ^{99m}Tc-DISIDA into the gastrointestinal tract was delayed but present in four patients with neonatal hepatitis. Gastrointestinal tract excretion was present in one and absent in the other two patients with severe neonatal hepatitis. No gastrointestinal tract excretion was identified in seven patients with biliary atresia and the one patient with a choledochal cyst. There was normal hepatic extraction and accumulation of tracer in the porta hepatis in the patient with a choledochal cyst (fig. 5).

Discussion

Jaundice in the neonatal period has numerous causes. Conjugated hyperbilirubinemia that persists beyond the first month of life is usually due to biliary atresia or neonatal hepatitis [4]. Since these two entities have similar clinical, biochemical, and histologic features, differential diagnosis is extremely difficult. Classically, biliary atresia has been distinguished from neonatal hepatitis by surgical exploration with determination of biliary tract morphology and liver biopsy [4]. Operative cholangiography and liver biopsy are not completely accurate in distinguishing biliary atresia from neonatal hepatitis [5].

Landing [6] hypothesized that neonatal hepatitis and biliary atresia represent variable expressions of a progressive inflammatory liver disease, "infantile obstructive cholangiopathy." Although there may be an association between neonatal hepatitis and biliary atresia [7], it is important to distinguish between these two broad groups for proper therapy. Intrahepatic cholestatic jaundice due to neonatal hepatitis, infectious disease, metabolic abnormalities, or enzymatic defects may be treated medically or managed conservatively. Biliary obstruction due to either biliary atresia or choledochal cyst requires prompt surgical intervention. The Kasai procedure of hepatic portoenterostomy permits sustained bile drainage in over 90% of patients operated on during the first 2 months of life [1]. Less than 20% of patients will have successful bile drainage by this procedure if surgery is delayed beyond age 3 months [1].

Neonatal hepatitis is a clinical syndrome with its onset between 1 and 4 weeks of age. Pathologic features are varied but usually include multinucleated giant cells, parenchymal

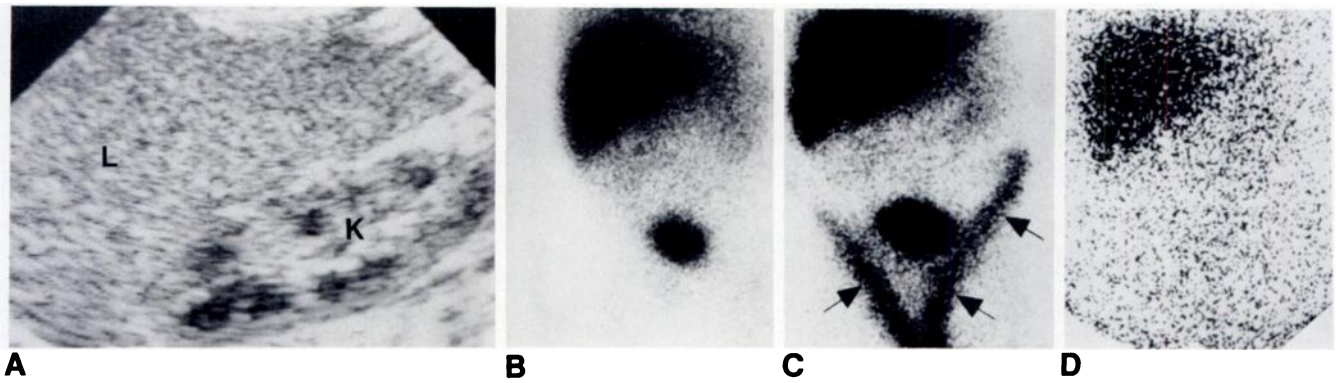

Fig. 2.—Biliary atresia in 8-week-old boy. **A**, Longitudinal sonogram through liver (L) and right kidney (K). No identifiable gallbladder. Hepatobiliary scintigrams at 5 min (**B**), 1 hr (**C**), and 20 hr (**D**). Normal hepatic extraction. No activity within gastrointestinal tract, even on delayed images. Shift of tracer activity to urinary tract, with artifact due to activity in urine in diaper, at 1 hr (**C**, *arrows*).

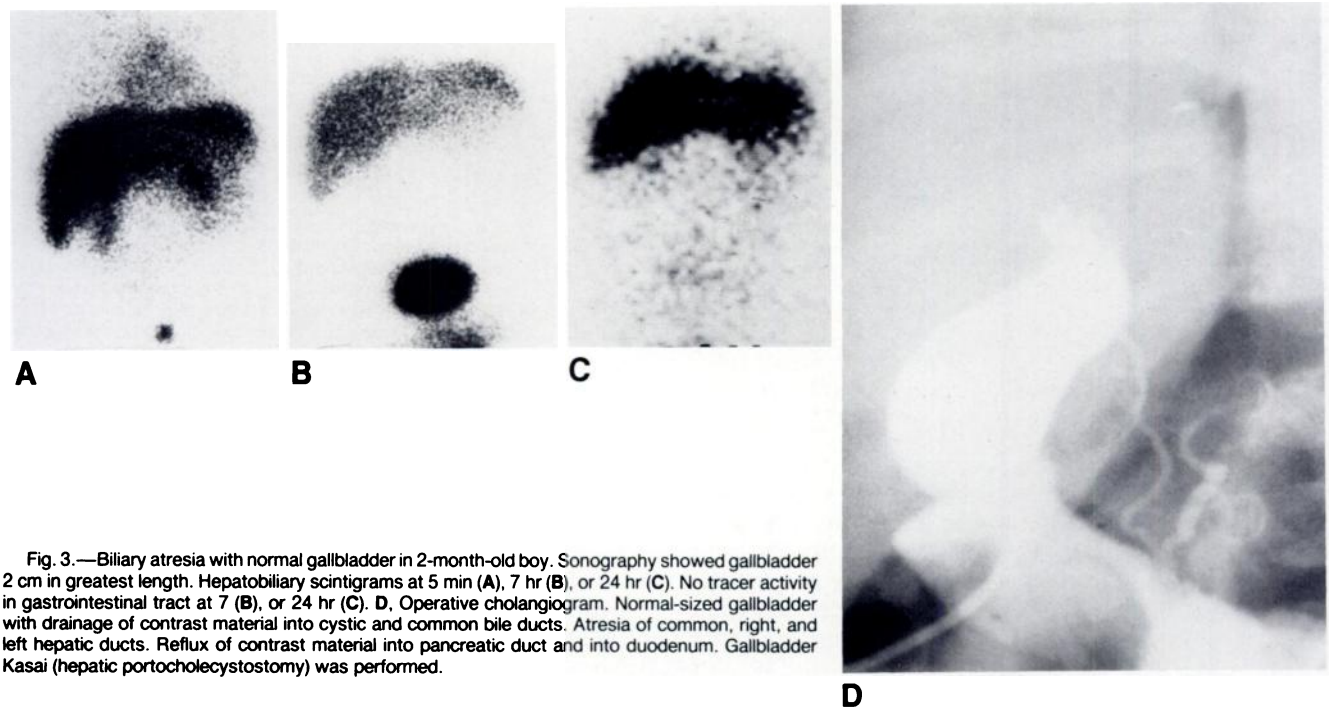

Fig. 3.—Biliary atresia with normal gallbladder in 2-month-old boy. Sonography showed gallbladder 2 cm in greatest length. Hepatobiliary scintigrams at 5 min (**A**), 7 hr (**B**), or 24 hr (**C**). No tracer activity in gastrointestinal tract at 7 (**B**), or 24 hr (**C**). **D**, Operative cholangiogram. Normal-sized gallbladder with drainage of contrast material into cystic and common bile ducts. Atresia of common, right, and left hepatic ducts. Reflux of contrast material into pancreatic duct and into duodenum. Gallbladder Kasai (hepatic portocholecystostomy) was performed.

disruption, and bile-duct canaliculi that are relatively free of bile [4]. Neonatal hepatitis may be due to a number of infectious agents (virus, Protozoa, spirochetes) or metabolic causes (α_1-antitrypsin deficiency, familial recurrent cholestasis, other errors of metabolism).

The sonographic features of neonatal hepatitis are nonspecific. Liver echogenicity is normal; liver size is either normal or increased. Both intra- and extrahepatic bile ducts are normal in caliber. Patients with neonatal hepatitis may have a gallbladder that is large (fig. 1), normal, small (fig. 4A), or not seen. Hepatobiliary scintigraphy after phenobarbital pretreatment demonstrates normal hepatic extraction and delayed tracer excretion into the gastrointestinal tract (fig. 1). If there is severe hepatocellular damage in patients with neonatal hepatitis, the hepatic extraction of tracer activity is decreased (figs. 4B–4D).

Biliary atresia is that component of obstructive cholangiopathy in which there is sclerosing cholangitis of the extrahepatic ducts [4]. Pathologically, the liver characteristically shows periportal fibrosis and intrahepatic, small bile-duct proliferation, with focal or total absence of the extrahepatic bile ducts. There is usually bile within bile-duct canaliculi. Multinucleated giant cells are less numerous than in neonatal hepatitis but may be present.

The sonographic findings of biliary atresia are also nonspecific. The liver has normal echogenicity and may be of normal size or enlarged. Both intra- and extrahepatic bile ducts are of normal caliber. Bile duct dilatation does not occur in biliary

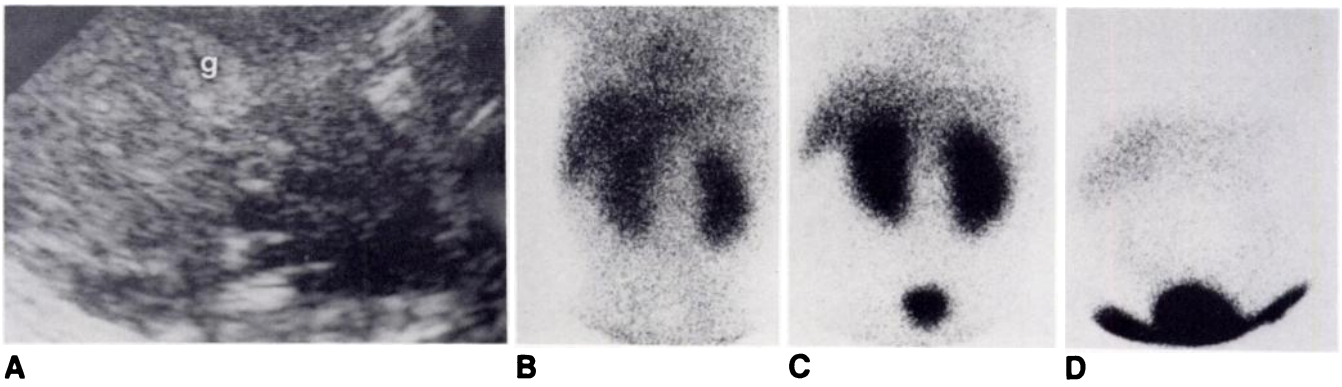

Fig. 4.—Neonatal hepatitis with severe hepatocellular damage in 9-week-old boy. **A**, Longitudinal sonogram. Small gallbladder (g). Hepatobiliary scintigrams at 5 min (**B**), 1 hr (**C**), and 6 hr (**D**). Liver activity is only slightly greater than cardiac blood pool at 5 min (**B**) and 1 hr (**C**), indicating poor hepatic extraction. Increased shunting of tracer to urinary system. No activity within gastrointestinal tract at 6 hr (**D**).

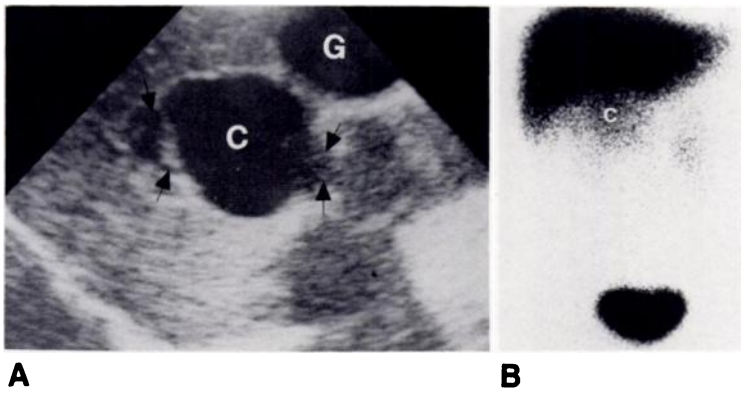

Fig. 5.—Choledochal cyst. **A**, Longitudinal sonogram through liver. Dilated cystic structure (C) appears to communicate with dilated bile ducts (*arrows*). Gallbladder (G) is somewhat distended. **B**, Hepatobiliary scintigram 8 hr after injection of ^{99m}Tc-DISIDA. Tracer accumulation within choledochal cyst (C). Tracer activity within kidneys and bladder, but no activity within gastrointestinal tract.

atresia despite distal obstruction, since the more proximal intra- and extrahepatic bile ducts are diseased and contracted [6]. The gallbladder in patients with biliary atresia is usually small or absent (fig. 2A). It has been stated that the sonographic demonstration of a normal gallbladder (length ≥ 1.5 cm) supports the diagnosis of neonatal hepatitis rather than biliary atresia [8]. However, two of our patients with proven biliary atresia had normal-sized gallbladders (fig. 3D). The identification of a small gallbladder (<1.5 cm long) has no predictive value in distinguishing biliary atresia from neonatal hepatitis [8]. Hepatobiliary scintigraphy with phenobarbital pretreatment is diagnostic of biliary atresia [2, 3]. All five of our patients under 3 months of age with biliary atresia had normal hepatic extraction with no excretion of tracer into the gastrointestinal tract (figs. 2B, 2C, and 3A–3C). After age 3 months, patients with biliary atresia may have decreased hepatic extraction with associated absence of tracer excretion into the gastrointestinal tract.

Choledochal cyst is a localized dilatation of the common bile duct with obstruction of biliary flow into the duodenum. Although the cause of choledochal cyst is unknown, it is probably in the spectrum of biliary atresia when present in the neonatal period. Older infants and children presumably develop choledochal cyst secondary to an anomalous relation between the common bile duct and the pancreatic duct [4].

The combination of hepatobiliary sonography and scintigraphy are diagnostic of choledochal cyst. Sonography shows a large, cystic mass in the porta hepatis with dilated bile ducts (fig. 5A). Although this sonographic finding is highly suggestive of choledochal cyst, it is critical to confirm that the cystic mass communicates with the biliary system functionally as well as anatomically. Hepatobiliary scintigraphy demonstrates normal hepatic extraction of ^{99m}Tc-DISIDA with delayed accumulation of tracer in the porta hepatis (fig. 5B). The severity of biliary obstruction is determined by the amount of tracer excretion into the gastrointestinal tract.

Real-time sonography is excellent for demonstrating hepatobiliary anatomy in patients with persistent neonatal jaundice. After fasting, the presence or absence of the gallbladder can be determined. A gallbladder longer than 3 cm suggests neonatal hepatitis. The diagnosis of choledochal cyst may be suggested.

Hepatobiliary scintigraphy with phenobarbital pretreatment is a sensitive, specific, and accurate method of distinguishing among neonatal hepatitis, biliary atresia, and choledochal cyst [3, 9]. The final diagnosis and subsequent therapy of persistent neonatal jaundice is determined by hepatobiliary function: hepatic extraction and excretion of tracer into the gastrointestinal tract. Hepatobiliary scintigraphy without phenobarbital pretreatment is sensitive (97%) and specific (82%) for biliary

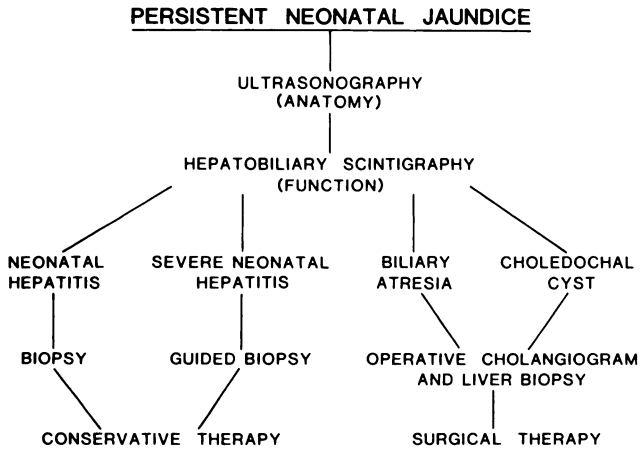

Fig. 6.—Diagnostic imaging and therapeutic approach to persistent neonatal jaundice.

atresia [9]. Majd et al. [2, 3] have shown that phenobarbital enhancement decreases the number of indeterminate and false-positive hepatobiliary scintigraphic studies in patients with persistent neonatal jaundice by enhancing tracer conjugation and excretion as well as increasing bile flow [10, 11]. The administration of phenobarbital to neonates with cholestatic jaundice with patent extrahepatic biliary ducts enhances and accelerates biliary excretion of ^{99m}Tc-IDA analogues [2, 3]. However, it has no effect on excretion of these compounds in neonates with extrahepatic obstruction due to biliary atresia or choledochal cyst.

The accuracy of ^{99m}Tc-DISIDA hepatobiliary scintigraphy depends on assessment of both hepatic extraction (uptake) and excretion of tracer [2, 3, 9]. Poor hepatic extraction in infants younger than 3 months indicates severe neonatal hepatitis rather than biliary atresia. This may be associated with (one patient) or without (two) demonstrable biliary excretion. Poor hepatic uptake in infants older than 3 months may be due either to severe neonatal hepatitis or to biliary atresia.

Our current evaluation of persistent neonatal jaundice includes sonography and hepatobiliary scintigraphy (fig. 6). If the gallbladder is enlarged on sonography, this is suggestive of neonatal hepatitis. A cystic porta-hepatis mass with bile duct dilatation on sonography is highly suggestive of choledochal cyst. In summary, sonography is initially performed to assess anatomy while the patient is receiving phenobarbital pretreatment for subsequent hepatobiliary scintigraphy.

Radionuclide scintigraphy is the most important step in the diagnostic evaluation of persistent neonatal jaundice (fig. 6) because it assesses hepatobiliary function. Hepatobiliary scintigraphy can distinguish neonatal hepatitis from biliary atresia in infants younger than 3 months. Although the Kasai procedure is rarely successful in older infants, surgical exploration is usually performed to distinguish between severe neonatal hepatitis and biliary atresia in infants older than 3 months. Hepatobiliary scintigraphy will confirm that a choledochal cyst communicates with the biliary system.

Patients with neonatal hepatitis or severe neonatal hepatitis should have a closed or guided liver biopsy before conservative therapy (fig. 6). Patients with biliary atresia or choledochal cyst should have operative cholangiography and liver biopsy before definitive surgical therapy (fig. 6). Expedient application of this hepatobiliary imaging approach is recommended for the evaluation of persistent neonatal jaundice.

ACKNOWLEDGMENT

We thank Jacqueline D. Wright for help in manuscript preparation.

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