Hepatobiliary Scintigraphy in Infancy

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J Nucl Med 1998; 39:311–319

Assessment of the hepatobiliary system by nuclear medicine techniques in the infant < 12 mo of age is usually indicated to help determine the etiology of jaundice. The majority of cases occur in children in the first 3 mo of life. This article primarily addresses the use of hepatobiliary scintigraphy in the neonatal period, but it also identifies other conditions that can occur in the first 12 mo of life.

Hyperbilirubinemia in the neonatal period is common, and, in the majority of cases, is due to benign physiological jaundice, a self-limiting condition. Persistent jaundice beyond 2 wk of age in full-term infants and 3 wk in preterm babies is not physiological, however, and evaluation of these patients must be undertaken (*1–3*). Cholestasis or prolonged elevation of serum conjugated bilirubin is always pathological. Cholestasis can be attributed to either intrahepatic causes of an infectious, metabolic or genetic nature or extrahepatic abnormalities causing mechanical obstruction to bile flow. Specific etiologies are discussed in detail in many major texts (*1–3*).

The diagnosis of biliary atresia in the neonatal period is often difficult. Its early diagnosis and the distinction of biliary atresia from other causes of jaundice are vital, as early intervention is paramount for the successful surgical correction of biliary atresia (*4,5*). Over the last 10 yr, we have performed 210 hepatobiliary scans in infants who were < 3 mo of age. The final diagnoses in this group were biliary atresia (40%), genetic/metabolic diseases (25%), infectious diseases (10%), Alagille syndrome (6%), cholestasis secondary to total parenteral nutrition (10%) and idiopathic neonatal hepatitis (9%).

Clinical features and standard laboratory tests of liver function cannot distinguish between disorders of hepatocellular dysfunction or those of the biliary tree. A diagnosis usually can be made after correlation of data from clinical information, imaging, liver biopsy and laboratory tests. A listing of investigations of neonatal hyperbilirubinemia is presented in Table 1.

TABLE 1
Investigations of Neonatal Hyperbilirubinemia

Liver function tests, bile acids
Coagulation profile
TORCH titers, VDRL, Hepatitis B surface antigen
Alpha-1-antitrypsin phenotype
Metabolic screen (urine amino acids, organic acids and succinylacetone)
Thyroid function tests
Red blood cell galactose 1-phosphate uridyltransferase
Sweat chloride test
Ultrasound
Hepatobiliary scintigraphy
Liver biopsy
Cholangiography (percutaneous or intraoperative)

DIAGNOSTIC STUDIES

Ultrasound

Ultrasound is used as one of the first imaging modalities principally to visualize the anatomy of the hepatobiliary system and exclude congenital abnormalities of the liver and biliary system (*6*). The abnormality most commonly diagnosed by ultrasound is congenital bile duct dilatation or choledochal cyst. Ultrasound also can be used to diagnose situs anomalies, vascular anomalies, polysplenia and asplenia. Asplenia may accompany biliary atresia. Ultrasound, however, is unable to diagnose biliary atresia. The size and contractility of the gallbladder may be assessed. Gallstones may present in the neonatal period and infancy, and ultrasound may diagnose biliary stones and sludge. Accuracy in identifying gallstones in the neonatal period is approximately 90%. However, the diagnosis of biliary sludge and inspissated bile causing biliary obstruction is less accurate (*2,7*).

Hepatobiliary Scintigraphy

The recommended hepatobiliary tracers for hepatobiliary scintigraphy are those of the ^{99m}Tc-labeled iminodiacetic (IDA) radiopharmaceutical group (*8–11*). These agents are transported to the liver bound to albumin and are actively taken up by the hepatocytes. Excretion into the bile ducts is by both active and passive transport mechanisms. Depending on the agent, 2%–15% is excreted by the kidneys. With increasing hepatocellular dysfunction, a higher percentage of tracer is excreted through the renal pathway (*11*).

Technetium-99m-diisopropyl-IDA (DISIDA) is most commonly used in hepatobiliary scintigraphy. The dose is 120 MBq adjusted to body weight or 15 MBq/kg with a minimum dose of 10 MBq and a maximum of 120 MBq. Technetium-99m-DISIDA has a hepatic extraction of 88% and urinary excretion of 11%.

Technetium-99m-trimethylbromo-IDA (mebrofenin) is administrated according to body weight with a minimum dose of 30 MBq and maximum dose of 185 MBq. Mebrofenin has a hepatic extraction of 98% and urinary excretion of 1.5%. Mebrofenin is currently the best agent for use with high bilirubin levels because it has a greater resistance to displacement by bilirubin (*11*). Mebrofenin has a > 70% hepatocyte uptake with bilirubin levels > 20 mg/dl, whereas DISIDA has a lower uptake of 36% with bilirubin levels of 10 mg/dl (*8,11*). A high-resolution collimator is used on a gamma camera with the energy peak set at 140 keV with a 20% window.

Fasting for a minimum of 3 hr is recommended. In neonates being investigated to differentiate between intrahepatic and extrahepatic causes of cholestasis, premedication with phenobarbitone for a minimum of 5 days in a dose of 5 mg/kg/day

Guest Editor: S. Ted Treves
Received May 13, 1997; accepted Oct. 1, 1997.
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orally is recommended. Phenobarbitone induces microsomal enzymes and increases bilirubin conjugation and excretion. This ensures the best possible excretion of hepatobiliary agents and visualization of the biliary tree. Majd et al. (*12*) recommends a blood level of 15 mg/dl for maximum effect. If the study is considered urgent, it could be performed without premedication. If no bowel activity is found, then the study should be repeated after phenobarbitone premedication. Care should be taken if the patient has fasted for > 24 hr or has been on total parenteral nutrition for extended periods. This may cause failure of visualization of the gallbladder. Prolonged fasting results in gallbladder atony and increased intraluminal gallbladder pressure from retained bile and sludge, secondary to the absence of endogenous cholecystokinin (*13*). Fasting, however, should not cause absent or reduced flow into the duodenum.

A gamma camera is placed anteriorly over the infant's abdomen and positioned to include the heart, liver and bowel. The radiopharmaceutical injection is given as a bolus in the antecubital fossa or back of the hand. The feet veins should be avoided if possible as this will prolong the bolus and invalidate quantitation (*14*). Data acquisition is started as soon as the injection is commenced.

The acquisition parameters are as follows:

1. Two-phase dynamic in 128-word matrix. Phase 1 = 3 sec/frame for 20 frames; Phase 2 = 60 sec/frame for 60 frames.
2. Magnification may be necessary in neonates and smaller infants (1.5× or 2×).
3. Spot views are performed 1 hr postinjection on both the anterior and right lateral views.
4. If no gastrointestinal activity is seen at 1 hr, the scan is repeated at 3–4 hr.
5. If bowel activity is still not seen at 3–4 hr, a SPECT study of the abdomen is performed.
6. If bowel activity remains undetectable at 24 hr, omit morning feeding until images are acquired to reduce bowel emptying. Anterior and lateral positions (10-min static images) are performed to determine activity in bowel or rectum.
7. Gallbladder function is assessed with a fatty meal or cholecystokinin. In neonates, if the gallbladder has been visualized, a normal feeding is given to assess gallbladder function and quantitate gallbladder ejection fraction. In older infants, a fatty meal or cholecystokinin also may be given (*10*). Cholecystokinin should be infused over a 20-min period and data collected for 30 min (2 frames/min). Infusion of cholecystokinin over a shorter period (1–3 min) may cause side effects of cramping and abdominal pain.
8. Hepatic extraction fraction (HEF) is defined by the extraction of tracer by the liver and reflects hepatocyte function and may be assessed visually and quantitatively. Visual inspection usually gives the diagnostic information required to differentiate conditions causing reduced hepatocyte function such as neonatal hepatitis and those with preserved hepatocyte function such as biliary atresia. In some equivocal cases, quantitation by HEF will add information to help differentiate biliary atresia, and it is useful for determining the degree of liver dysfunction semiquantitatively. The HEF is calculated from the hepatic phase of the study and is a measure of the efficiency of the hepatocyte in extracting the radiopharmaceutical from the blood. The technique uses a Fourier transform deconvolution method and is the ratio of the initial hepatocyte uptake divided by the peak vascular uptake (*14,15*).

$$\text{HEF} = \frac{\text{y intercept exponential fit liver response curve}}{\text{y max data value liver response curve}}. \quad \text{Eq. 1}$$

The normal HEF in a pediatric population is 92% (*14*).
9. Hepatic half clearance times ($T_{1/2}$) are defined as hepatic parenchymal clearance/excretion and can be quantitatively assessed by determining the $T_{1/2}$ from a peripheral region of liver parenchyma. The region of interest should exclude major bile ducts when posssible. The excretion $T_{1/2}$ is calculated by a least squares fit to the clearance curve. There is a large overlap of $T_{1/2}$ in the neonatal period, and we have not found it to be an accurate method to differentiate biliary atresia from other forms of cholestasis (*14–16*).

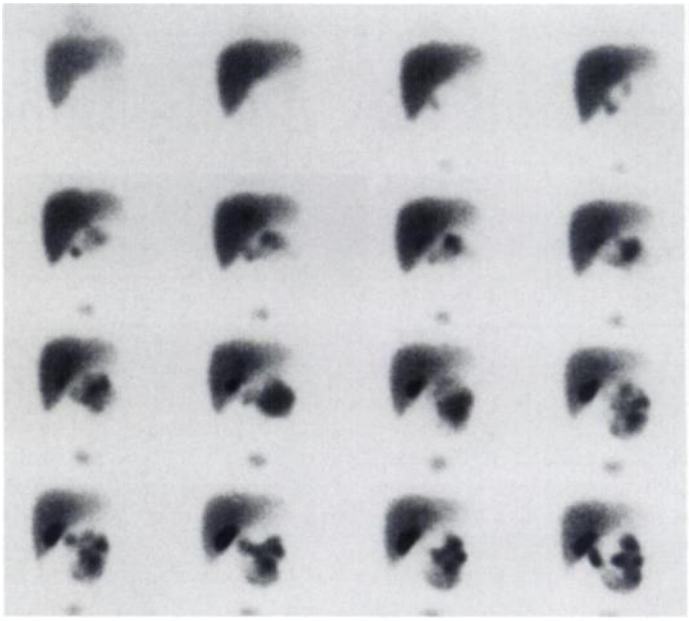

FIGURE 1. Normal hepatobiliary scan. Two-minute images in a 4-wk-old male infant with mild jaundice. There is good extraction with a HEF of 100%. Clearance of tracer from the cardiac blood pool and excretion of tracer with activity passing freely into the duodenum at 8 min and gallbladder activity seen at 12–14 min.

Image Interpretation. Interpretation of the hepatobiliary scan should be made relating to the following parameters: blood flow and extraction of tracer by liver (uniformity, defects and HEF); time of excretion and visualization of biliary tree; time of gallbladder activity; dilatation of biliary tree (hepatic, secondary, tertiary and common bile ducts); time of visualization of tracer in duodenum; parenchymal clearance (segmental and uniform); gallbladder contractility; duodenogastric reflux; delayed images of bowel activity or rectal activity; and position of small bowel (*17*).

Normal Hepatobiliary Scintigraphy in Infants. In neonates, extraction of tracer by the liver is prompt and has a uniform distribution, which reaches a maximum tracer accumulation within 5 min. The gallbladder may be visualized as early as 10 min, but occasionally it is not seen in the neonatal period. The significance of a nonfunctioning gallbladder in the neonatal period is uncertain but most likely represents biliary stasis and reduced bile flow. Bowel activity is seen usually by 30–40 min. The hepatic, cystic and common bile ducts are not normally visualized in the neonatal period (Fig. 1). From 12 mo of age the hepatic, cystic and common bile ducts become more obvious; however, the prominence of left hepatic bile ducts as

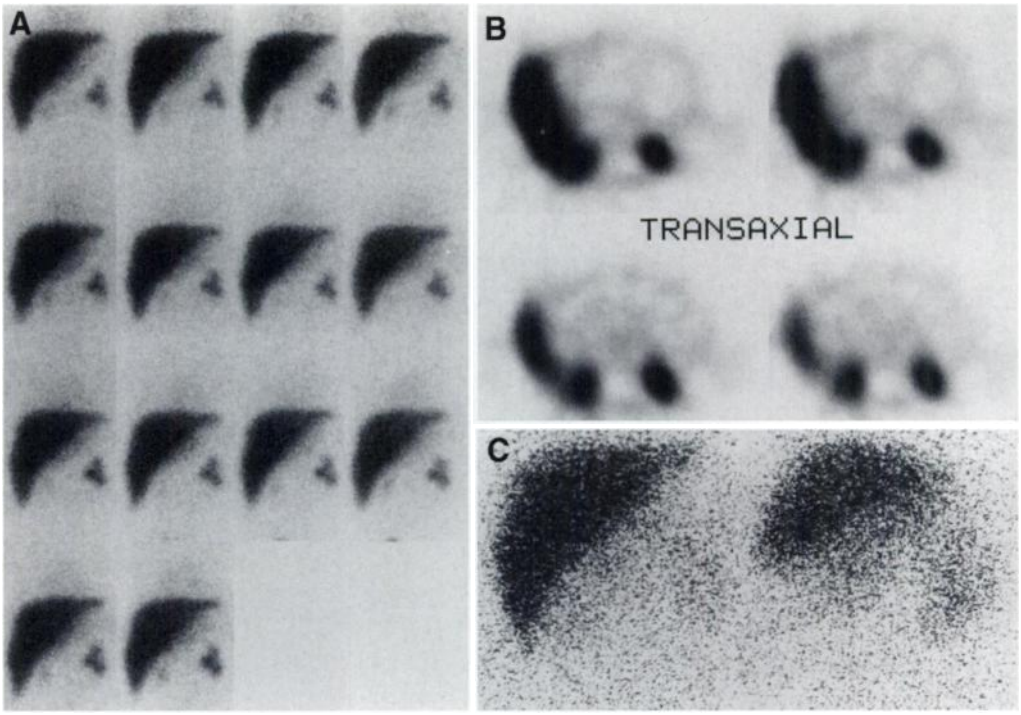

FIGURE 2. Biliary atresia. A 6-wk-old male infant presented with jaundice and acholic stools. The hepatobiliary scan shows good extraction with a HEF of 100%. At 1 hr (A), 4 hr with SPECT (B) and 24 hr (C), there is persisting parenchymal uptake with no activity visualized in the abdomen.

seen in adults is not usually seen until after the age of 8 yr. The normal HEF is > 92%, and hepatic $T_{1/2}$ from the liver parenchyma is normally < 37 min (*14*).

Liver Biopsy

Percutaneous liver biopsy is often used in the investigation of cholestasis (*2,3,18*). Liver biopsy has been reported to correctly diagnose biliary atresia in 60%–90% of patients (*6,18*). The findings of fibrosis, bile duct proliferation, giant-cell transformation and canalicular bile stasis with an intact basic lobular architecture are most consistent with biliary atresia. In neonatal hepatitis, there is severe hepatocellular disease, with infiltration by inflammatory cells and focal areas of necrosis. However, histologic similarities occasionally exist between biliary atresia and neonatal hepatitis, making the diagnosis difficult. In these instances, surgical exploration of the portal region is indicated. Histologic changes similar to those of neonatal hepatitis occur in many of the other metabolic diseases causing cholestasis.

Cholangiography

A cholangiogram may be performed to diagnose biliary atresia and other congenital abnormalities if the other investigations are nondiagnostic. The cholangiogram usually is performed as part of an exploratory laparotomy, but it may be performed percutaneously. Cholangiography may help to identify the presence of the gallbladder, the patency of the biliary tree, dilatation of the bile ducts or the site of obstruction (*6*).

CLINICAL CONDITIONS CAUSING CHOLESTASIS

Neonatal cholestasis may be caused by many conditions (*2,3,6*). Many of the metabolic, endocrine and infectious causes may be excluded by clinical and laboratory findings. Congenital dilatation of the biliary tree or choledochal cysts usually are detected by ultrasound examination and confirmed by scintigraphy (*6*). The causes of cholestasis in the majority of cases remain unclear. The distinction of biliary atresia from neonatal hepatitis may be clinically difficult, and biochemical tests usually are inconclusive. Hepatobiliary scintigraphy should be incorporated early into the investigative workup of hyperbilirubinemia as it plays an important role in the early diagnosis of biliary atresia and differentiation of other causes of cholestasis (*6,8–10,12,19*).

Biliary Atresia

The pathogenesis of biliary atresia remains unknown (*1–3*). In the majority of infants, obstructive obliteration of the biliary tree occurs peri- or postnatally (*20*). Histopathology shows both chronic and acute inflammatory changes, and the process may be progressive, as the pathology has been reported to continue after surgical relief of the obstruction (*1,5*). Extrahepatic anomalies are present in 10%–25% of cases. These include polysplenia, absent inferior vena cava, preduodenal or absent portal vein, anomalous hepatic artery, intestinal malrotation, bilobed lungs, congenital heart disease and transverse liver (*21,22*). It is important to identify biliary atresia as early as possible because the long-term outcome depends on early relief of biliary obstruction with establishment of adequate bile flow. Irreversible hepatic damage will develop if adequate bile flow is not established within 2–3 mo of life. According to a recent nationwide survey in Japan, long-term (> 10 yr) survival after diversionary surgery was reported in only 325 (16%) of 2013 patients. Only 7.8% remained jaundice free with normal liver function. Approximately 20% of patients without jaundice are able to survive for longer periods of time. However, most develop portal hypertension or abnormal liver function (*5*). Postoperative cholangitis continues to be a problem despite various antireflux procedures and long-term antibiotics.

Hepatobiliary Scan Findings. Hepatobiliary scan findings have been shown to be an effective method of differentiating biliary atresia from the other causes of cholestasis (*6,8–10,12,17,23–25*). Typically, patients with biliary atresia who present within the first 2 mo of life show prompt hepatic extraction with a HEF > 92%, nonvisualization of the gallbladder, prolonged retention of tracer in the liver and no excretion of tracer into the bowel at 1, 4 and 24 hr (Fig. 2).

Patients presenting at >3 mo of age usually have compromised hepatocyte function and show reduced hepatic extraction, reflected by a reduction in HEF, and no biliary excretion. In this situation, differentiation from severe neonatal hepatitis or cholestasis is more difficult. There have also been case reports of

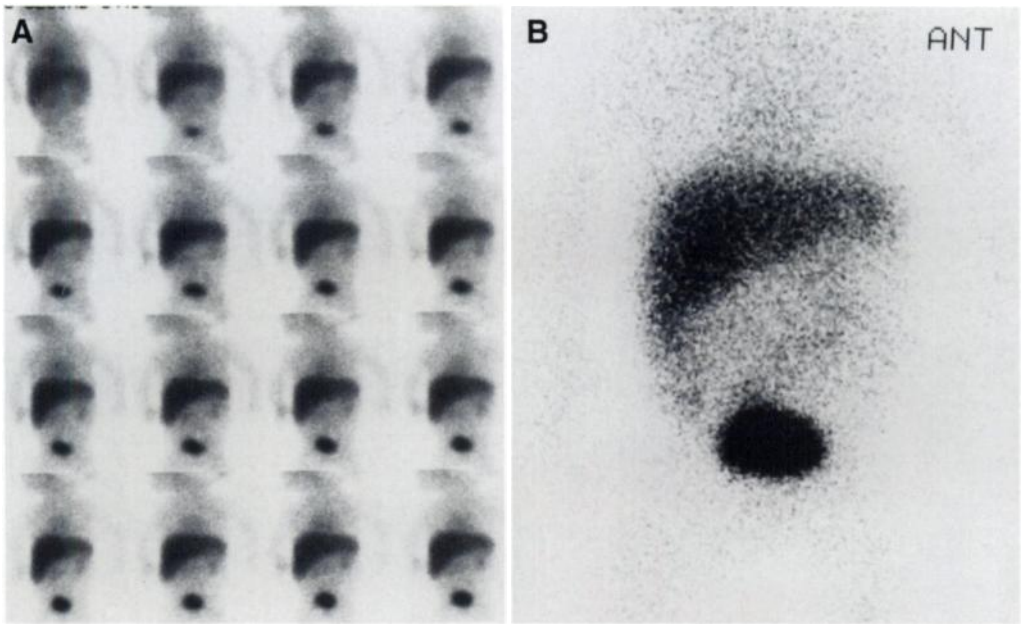

FIGURE 3. Neonatal hepatitis. A 7-wk-old female infant with persistent jaundice and conjugated hyperbilirubinemia. The biliary scan reveals reduced clearance from the cardiac blood pool and reduced extraction of tracer. There is possibly a small amount of activity seen in the small bowel at 60 min (A). Delayed images at 4 hr show definite activity in the abdomen (B), excluding biliary atresia. There is still persistent cardiac blood-pool activity.

patients with biliary atresia where tracer was seen in the bowel in the early neonatal period, but repeat studies showed no biliary excretion (*26*). This pattern rarely occurs and most likely is due to the progressive nature of the obliteration of the bile ducts continuing after birth (*20*). In cases where there is good extraction of tracer by the liver and only minimal biliary excretion seen on hepatobiliary scan findings, close follow-up is recommended. The hepatobiliary scan should be repeated if jaundice remains and acholic stools are seen.

The sensitivity of scintigraphy for the diagnosis of biliary atresia was reported by Gerhold et al. (*23*) as 91% accuracy, 97% sensitivity and 82% specificity. In a study using mebrofenin, Ben Haim et al. (*19*) described 6% false-positive studies for biliary atresia and no false-negatives. Majd et al. (*12*) reported a sensitivity of 100% and a specificity of 70%. Specificity was increased by premedication with phenobarbitone (5 mg/kg/day for 5 days). Majd et al. (*12*) increased the specificity from 68% to 94% after 5 days of phenobarbitone, which achieved blood levels of 15 mg/dl in a prospective study of 46 infants (*12*). This appears to be the optimal blood level for maximum enhancement of the hepatobiliary study.

In 2 yr, there were 24 patients referred for hepatobiliary studies using ^{99m}Tc-DISIDA at the Royal Alexandra Hospital for Children in Sydney to differentiate biliary atresia from other causes of cholestasis. In these studies, there was 100% sensitivity and 86% specificity for the diagnosis of biliary atresia. One patient with Alagille syndrome, one case of severe cholestasis secondary to total parenteral nutrition and one case of severe neonatal hepatitis showed no excretion over 24 hr, and biliary atresia could not be excluded on the basis of the scan. Although scintigraphic proof of biliary excretion rules out biliary atresia, the absence of excretion is indeterminate and requires further investigation.

Neonatal Hepatitis

Neonatal hepatitis syndrome, which is managed medically and conservatively (*2,3*), or intrahepatic cholestasis can be considered in three groups:

1. Idiopathic neonatal hepatitis, which has an unknown etiology.
2. Infectious neonatal hepatitis, which is due to a specific agent (e.g., cytomegalovirus, hepatitis B, enterovirus or coxsackie virus. Sepsis from bacterial infections, especially pathogenic *E. coli* may cause hepatic dysfunction, and this may be compounded by the cholestatic effect of endotoxin (*2,3*).
3. Neonatal hepatitis from metabolic or genetic causes (e.g., alpha-1-antitrypsin deficiency).

Hepatobiliary Scan Findings. Majd et al. (*12*) described three scintigraphic patterns in infants with neonatal hepatitis. The patterns vary according to the severity of the cholestasis and hepatocellular disease.

1. Visualization of tracer in the bowel and/or gallbladder with or without impairment of hepatic extraction. This pattern excludes biliary atresia.
2. Absent excretion with reduced hepatic extraction. This pattern in the first 3 mo of life is inconsistent with biliary atresia and indicates severe parenchymal liver damage.
3. No excretion with normal or near-normal hepatic uptake. This pattern is consistent with biliary atresia, but has been described in some cases of severe neonatal hepatitis, cystic fibrosis and Alagille syndrome.

In patients with neonatal hepatitis, the HEF is generally reduced, reflecting the reduced hepatocyte extraction of tracer (*14*). There is persisting and delayed clearance of tracer from the blood-pool particularly evident by prolonged cardiac blood pool activity (Fig. 3). If the hepatocellular dysfunction is severe, some of these patients will also show absent excretion of tracer into the biliary tree over 24 hr. We have found 3–4-hr SPECT scans of the abdomen to be particularly helpful in detecting the small amounts of biliary excretion of tracer into the small bowel (Fig. 4) not evident on planar views. The presence of any such excretion rules out biliary atresia. Occasionally, 24-hr images are required and may show activity in the gut or rectum. Lateral views are useful to separate the pelvic activity of rectum and bladder. As the degree of liver dysfunction increases, there is a concurrent increase in renal excretion.

Congenital Bile Duct Dilatation (Choledochal Cyst)

Many patients present during the first months of life with cholestatic jaundice and acholic stools. The pathogenesis is controversial. Choledochal cysts have been reported in association with biliary atresia. Choledochal cysts have been classified into three major types: cystic, diverticular and choledochocele (*27*). Todani et al. (*28*) modified the classification

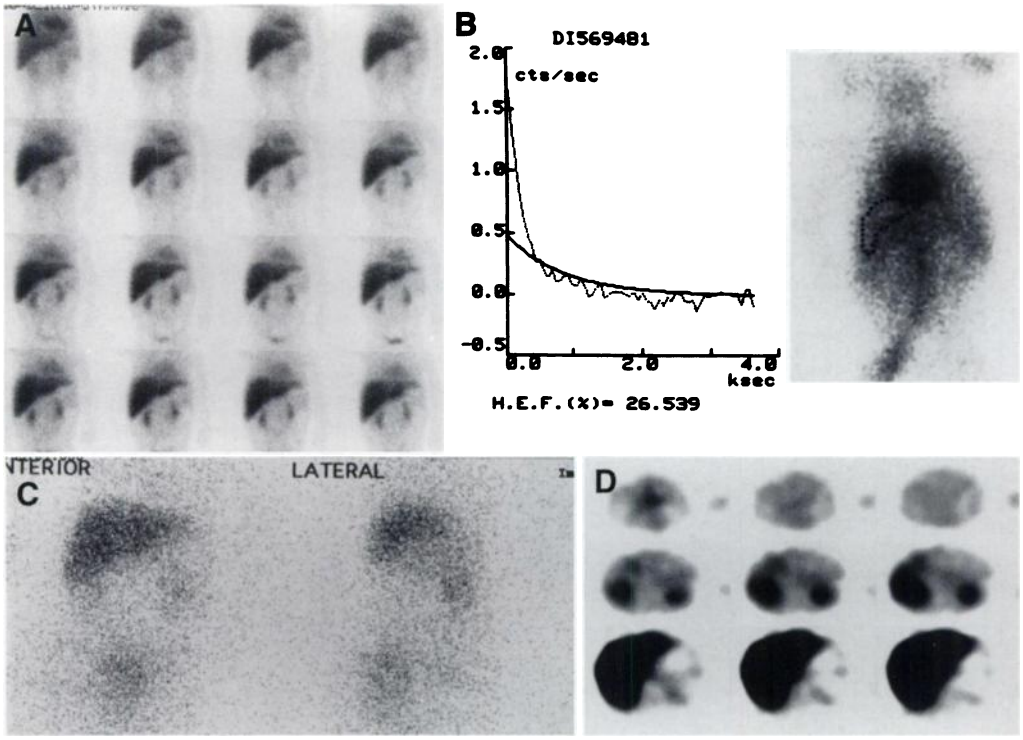

FIGURE 4. Severe neonatal hepatitis. A 6-wk-old male infant with positive cytomegalovirus titers and conjugated hyperbilirubinemia. The biliary scan shows severe reduction in hepatic uptake and persisting cardiac blood-pool activity (A). The HEF was low at 27% (B). Planar views at 4 hr show no evidence of bowel activity (C). SPECT of the abdomen at 4 hr, however, shows activity in the gastrointestinal tract (D).

into six types based on cholangiographic morphology and the number of intrahepatic and extrahepatic bile duct cysts:

Type IA = dilatation of the common bile duct with marked dilatation of part or all of the extrahepatic biliary tree and normal intrahepatic biliary tree. This form occurs in 80%–90% of cases.

Type IB = focal, segmental dilatation of the distal common bile duct.

Type IC = fusiform dilatation of the common bile duct with diffuse cylindrical dilatation of the common hepatic duct and common bile duct with normal intrahepatic biliary tree.

Type II = diverticulum of the common bile duct.

Type III = choledochocele of the intraduodenal portion of the common bile duct.

Type IVA = multiple cysts with dilatation of the intrahepatic and extrahepatic bile ducts.

Type IVB = multiple cysts of the extrahepatic ducts.

Type V or Caroli's disease = dilatation of one or several segments of the intrahepatic bile ducts without dilatation of the common bile duct (*29,30*).

Choledochal cysts can be associated with simple hepatic cysts, stone formation, cholangitis, pancreatitis, portal hypertension and biliary atresia. Ultrasound usually is the initial investigation, which reveals a cystic mass in the porta hepatis (*6*).

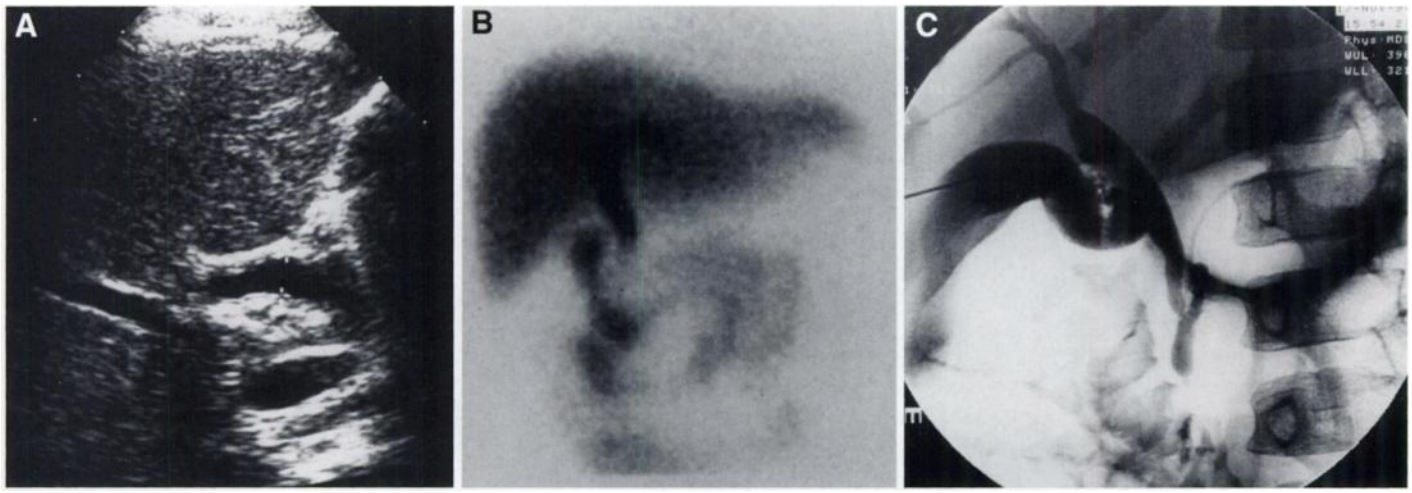

FIGURE 5. Congenital dilatation of the biliary tree (choledochal cyst). An 8-mo-old male infant presented with episodes of intermittent jaundice and abdominal pain. Ultrasound (A) reveals mild-to-moderate dilatation of the common bile duct. Hepatobiliary scintigraphy confirms (B) dilatation of the common bile duct and left hepatic duct, but no obstruction to bile flow was seen. Percutaneous cholangiogram via puncture of the gallbladder confirms the anatomical dilatation of the common bile duct and left hepatic duct (C).

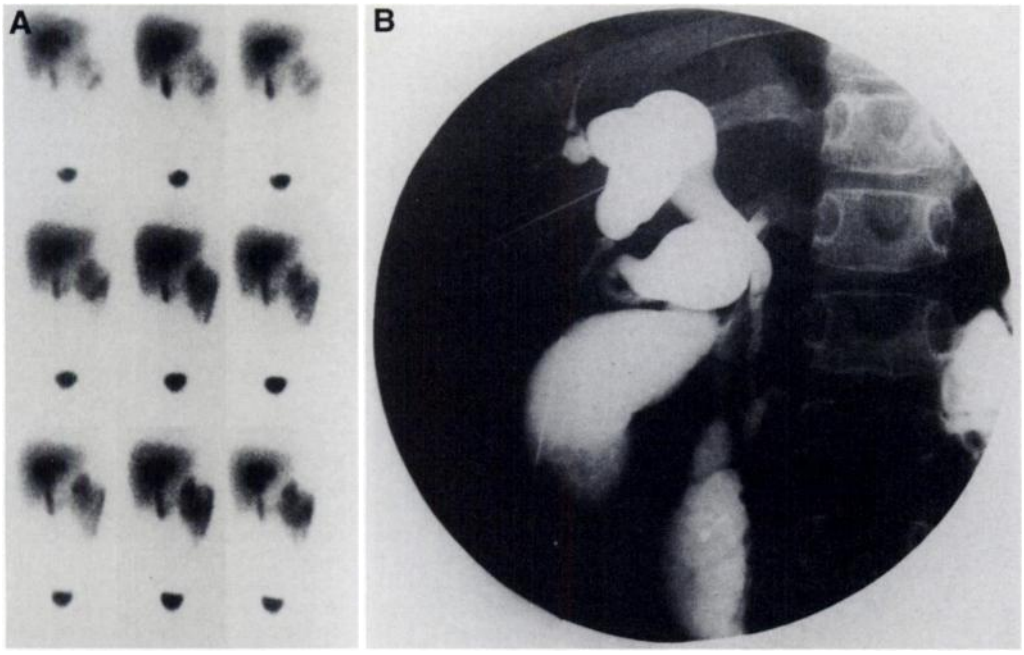

FIGURE 6. Large choledochal cyst. A 10-mo-old female infant presented with jaundice. Hepatobiliary scintigraphy (A) revealed marked dilatation of the main right and left hepatic ducts, upper common bile duct and cystic duct but tracer passed into the duodenum. Percutaneous cholangiogram (B) confirms the marked dilatation of the main hepatic ducts, cystic duct and upper common bile duct.

Hepatobiliary Scan Findings. Scintigraphy helps in differentiating the types of cystic dilatation of the bile ducts and determines whether the cystic structure communicates with the biliary system. The appearance of choledochal cysts ranges from mild dilatation of the common bile duct (Fig. 5) to cystic dilatation, which may involve major intrahepatic ducts and the cystic duct (Fig. 6). Extremely large cystic structures may obstruct biliary flow completely. Hepatobiliary scan appearance may be as follows:

1. Good extraction and excretion of tracer (HEF > 92%).
2. Photopenic area in porta hepatis depending on size of the anatomic abnormality.
3. Accumulation of tracer in the dilated ducts or cysts. This may occur early within normal time or be delayed for up to 24 hr.
4. Complete obstruction with negligible biliary flow and nonfilling of the cystic mass.
5. Choledochal cysts may contract with a stimulus of a fatty meal or cholecystokinin analog.
6. Activity in the peritoneal cavity. This is a rare complication due to rupture of the choledochal cyst.
7. Caroli's disease may present in infancy and shows a particular pattern of cystic dilatation with accumulation of tracer in the intrahepatic ducts of the biliary tree.

Congenital Cystic Abnormalities

With the frequent use of antenatal ultrasound, focal abnormalities in the liver may be detected. Liver cysts may occur, and whether these connect to the biliary system can be determined by hepatobiliary scan findings (*6*).

Hepatobiliary Scan Findings. The liver shows good perfusion and function with excretion of tracer into the biliary system. If there is connection of the cyst to the biliary system there initially may be a photon-deficient area seen in the early parenchymal phase of the study and delayed filling of the cyst with tracer (Fig. 7).

Spontaneous Perforation of the Bile Duct

Idiopathic perforation of the extrahepatic biliary system is uncommon, but it is the second most common cause of surgical jaundice in infants (*2*). Perforation occurs at the junction of the common duct and cystic duct. Presentation with jaundice and abdominal distension usually occurs in the first 1–2 wk of life.

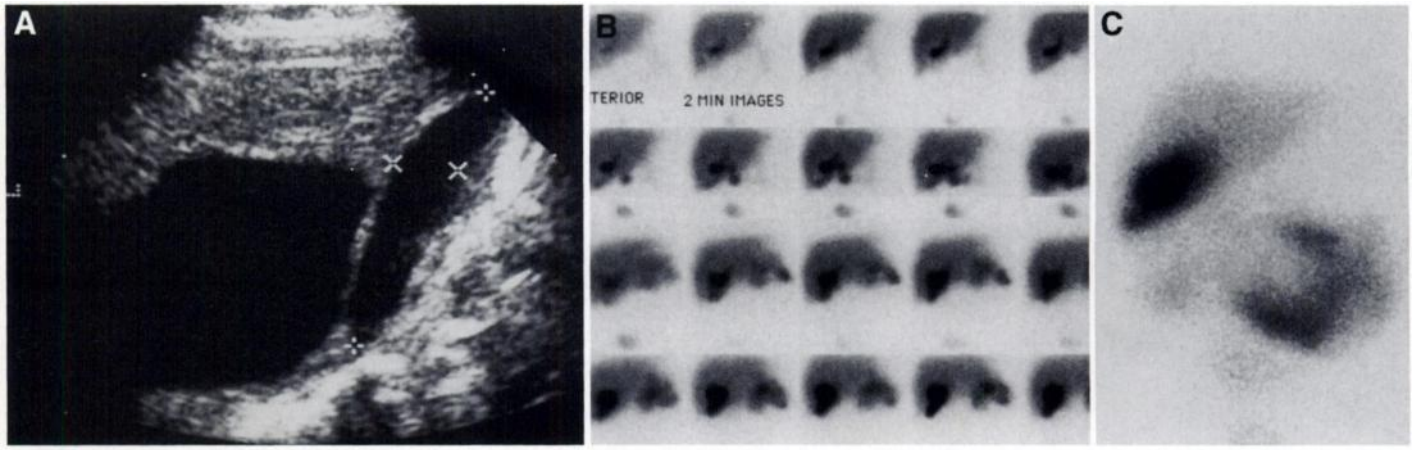

FIGURE 7. Congenital hepatic cystic mass. Antenatal ultrasound revealed a cystic mass close to the gallbladder. At 2 wk, an ultrasound (A) confirmed the cystic mass in the right lobe of the liver close to the gallbladder (markers). Biliary scan initially showed a photon-deficient area adjacent to the functioning gallbladder. Later images show filling of the cystic mass with tracer (B), indicating communication of the cyst with the biliary system. Delayed images at 3 hr (C) confirm retention of tracer in the mass with most of the tracer having cleared from the liver and biliary tree.

Ultrasound usually will identify a pseudocyst in the porta hepatis without dilatation of the biliary tree and occasionally sludge or stones in the common bile duct distal to the perforation site. Intraoperative cholangiography is performed to confirm the diagnosis at surgery (*6,9*).

Hepatobiliary Scan Findings. Scintigraphy may show a photopenic area caused by the pseudocyst with slow accumulation into the cyst or dispersion of tracer into the peritoneal cavity. The pseudocyst may enlarge to a size that causes compression of the extrahepatic bile ducts. The pseudocyst may also mimic a choledochal cyst on ultrasound. The pattern described cannot be differentiated from a ruptured choledochal cyst (*9,31,32*).

Bile-Plug Syndrome

In this condition, there is partial or complete obstruction of the extrahepatic biliary system by inspissated bile plugs. Patients with increased bile viscosity are at risk. Particularly infants with dehydration, cystic fibrosis, hemolytic disorders, total parenteral nutrition and infants after extensive ileal resections. The decreased solubility of bile leads to bile sludge and eventually to cholelithiasis or choledocholithiasis. Ultrasound usually demonstrates a distended gallbladder with or without sludge and gallstones. The intrahepatic biliary tree may be dilated, and the extrahepatic biliary tree may contain sludge (*2,9,33*).

Hepatobiliary Scan Findings. Scintigraphy shows a variable pattern. However, it usually shows good extraction of tracer by the liver with poor excretion into the gut, typical of severe cholestasis. Occasionally, however, there is reduced extraction similar to patients with hepatocellular dysfunction from neonatal hepatitis. In a small number of cases, no excretion is seen and the study is unable to differentiate biliary atresia (*9,34*).

Syndromatic Paucity of Intralobular Bile Ducts

Arteriohepatic Dysplasia or Alagille Syndrome. Alagille syndrome is characterized by paucity of interlobular bile ducts associated with congenital abnormalities (*35*). These include typical facial features, pulmonary artery stenosis, complex congenital heart disease and vertebral anomalies. There is also a nonsyndromic form of paucity of the interlobular bile ducts (*1–3*).

Hepatobiliary Scan Findings. Scintigraphy shows good extraction of the tracer but marked holdup in liver parenchyma similar to severe cholestasis with usually minimal excretion into the gut. Occasionally no excretion is seen, and in these patients scintigraphy cannot distinguish Alagille syndrome from biliary atresia (*8,36*).

Cystic Fibrosis

Hepatobiliary involvement in neonates with cystic fibrosis ranges from hepatomegaly or mild cholestatic jaundice to severe cholestasis with acholic stools. Clinically apparent liver disease is found in 35% of infants with cystic fibrosis. Histologic evidence of focal biliary cirrhosis was found in 10% of cystic fibrosis patients < 3 mo of age, and cholestasis was found in 38%. Biliary obstruction in neonates with cystic fibrosis is due mainly to inspissation of biliary secretions and generally resolves by 3–4 mo. Biliary atresia must be excluded if there are acholic stools. Over 50% of all cystic fibrosis patients have ultrasound and scintigraphic abnormalities of the biliary system, particularly relating to the gallbladder (*1,2*).

Hepatobiliary Scan Findings. Scintigraphy of cystic fibrosis patients in the neonatal period usually shows moderately good extraction of tracer with poor excretion. However, cholestasis may be severe and show no excretion into the gut. Premedication with phenobarbitone is highly recommended for this group of patients. Repeat studies may be necessary, or liver biopsy may be required to exclude biliary atresia. Later in life, the scans will show a range of abnormalities mainly relating to holdup of tracer in the bile ducts, usually the left hepatic ducts, a large or nonfunctioning gallbladder and stricture of the distal common bile duct (*8,9,36,37*).

Total Parenteral Nutrition

Severe cholestasis may occur due to prolonged total parenteral nutrition. The pathogenesis is multifactorial. The omission of oral feedings reduces the output of gastrointestinal hormones, which are normal stimulants to bile flow. The nutrient solution has potential toxicity. Other hepatotoxins include specific amino acids, metabolic or degradation products, copper and manganese. These infants are susceptible to recurrent bacterial infections, and endotoxins may be hepatotoxic. Ultrasonography may demonstrate distended gallbladder, fatty liver or sludge in the biliary tree (*2,3,6*).

Hepatobiliary Scan Findings. Scintigraphy shows variable tracer extraction and excretion. Most commonly found in this group is severe cholestasis with initially moderately good tracer extraction by the liver but no excretion. Repeat studies with phenobarbitone premedication are often required to show bile flow. In some patients, there is a significant reduction in hepatocellular function, and although the scan may be unable to show bowel activity, biliary atresia cannot be excluded (*6,8,9*).

Gallstones

The presence of gallstones in the first 12 mo of life is uncommon. However, sludge and gallstones may occur, causing obstruction to the biliary tree and poor gallbladder function. Ultrasound initially diagnoses the gallstones and sludge. Cholecystitis occurs in sick, premature infants who often have undergone prolonged fasting without frequent stimulation of gallbladder contraction and require prolonged total parenteral nutrition. Sepsis, abdominal surgery, blood transfusions, and the use of diuretics and narcotic analgesics are also compounding factors. Pigmented stones composed of cholesterol-calcium bilirubinate are the most common stone in the neonatal and infant period. Obstructive jaundice in infants has been reported secondary to brown pigment stones in the extrahepatic biliary tree and gallbladder. These stones occur due to bacterial hydrolysis of conjugated bilirubin. The bile usually cultures *E. coli* and bacteroides (*1,9*).

Hepatobiliary Scan Findings. Scintigraphy shows good extraction of tracer, usually with excretion into the biliary tree (Fig. 8). The study enables the assessment of gallbladder function by fatty meal or cholecystokinin stimulation if the gallbladder fills with tracer. Cystic duct obstruction is suspected when there is nonfilling of the gallbladder. There may be complete obstruction by stones of the biliary tree, and dilatation of the intrahepatic bile ducts and common bile duct may be demonstrated (*9,17*).

Metabolic Conditions

Metabolic causes of neonatal cholestasis are generally divided into three groups of disorders: (a) amino acid metabolism (e.g., tyrosinemia), (b) lipid metabolism (e.g., Wolman disease) and (3) carbohydrate metabolism (galactosemia and fructosemia) (*2,3*).

Hepatobiliary Scan Findings. These metabolic abnormalities cause hepatic dysfunction, and scintigraphy findings are similar to those of neonatal hepatitis associated with cholestasis. Usually, a small amount of biliary excretion is seen in the gut, excluding biliary atresia. Occasionally, the hepatic dysfunction

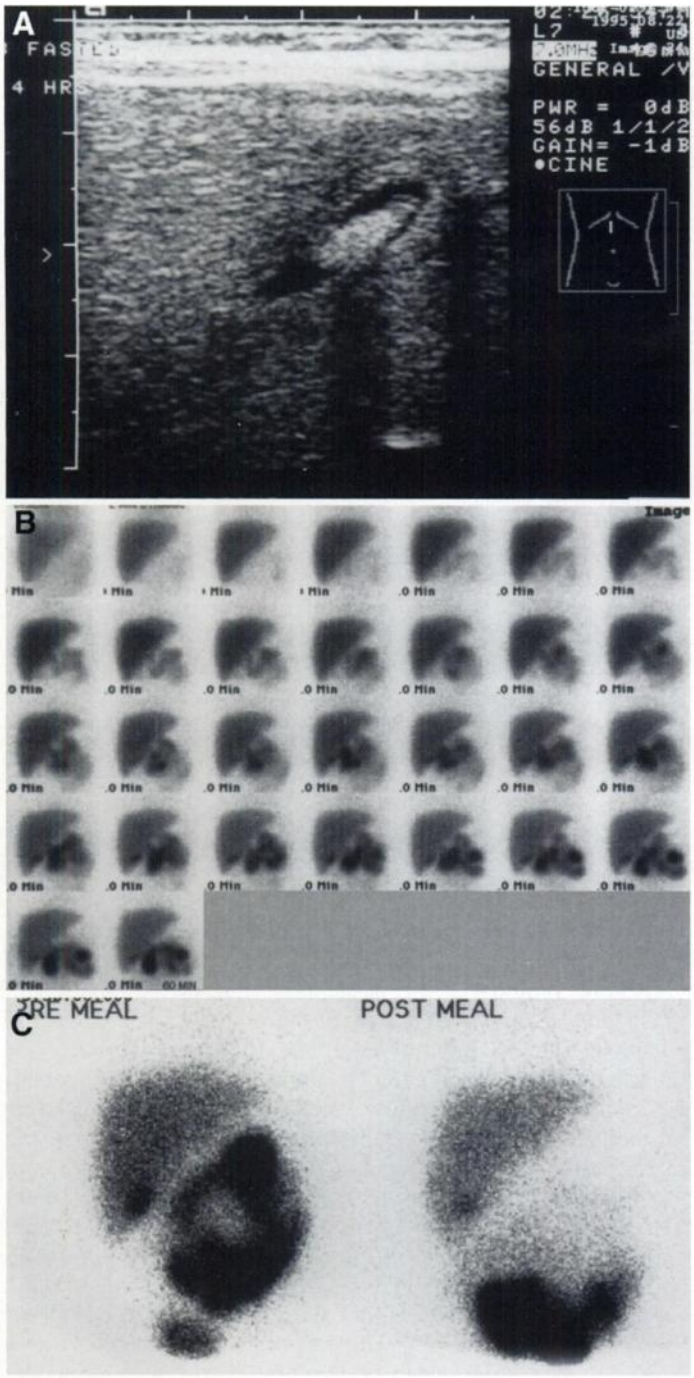

FIGURE 8. Gallstones. A 3-mo-old female infant presented with jaundice and conjugated hyperbilirubinemia that settled over several days. Ultrasound (A) shows a small gallbladder containing an echogenic stone. The hepatobiliary scan shows good extraction and excretion of tracer with a small functioning gallbladder (B), which contracted after a meal (C). There was no obstruction to bile flow.

is so severe that no tracer is visualized, and it is therefore impossible to exclude longstanding biliary atresia (*6*).

Hypopituitarism

Cholestasis has been reported with hypopituitarism. Jaundice, acholic stools in association with hypoglycemia, seizures or wandering nystagmus suggest hypopituitarism as the cause. The mechanism is unknown. However, it may be due to the deficiency of one or more hormones, which could delay the normal maturation of hepatic transport mechanisms or inhibit bile-acid synthesis, which would promote the accumulation of precursor bile acids, causing a cholestatic effect (*2,3*).

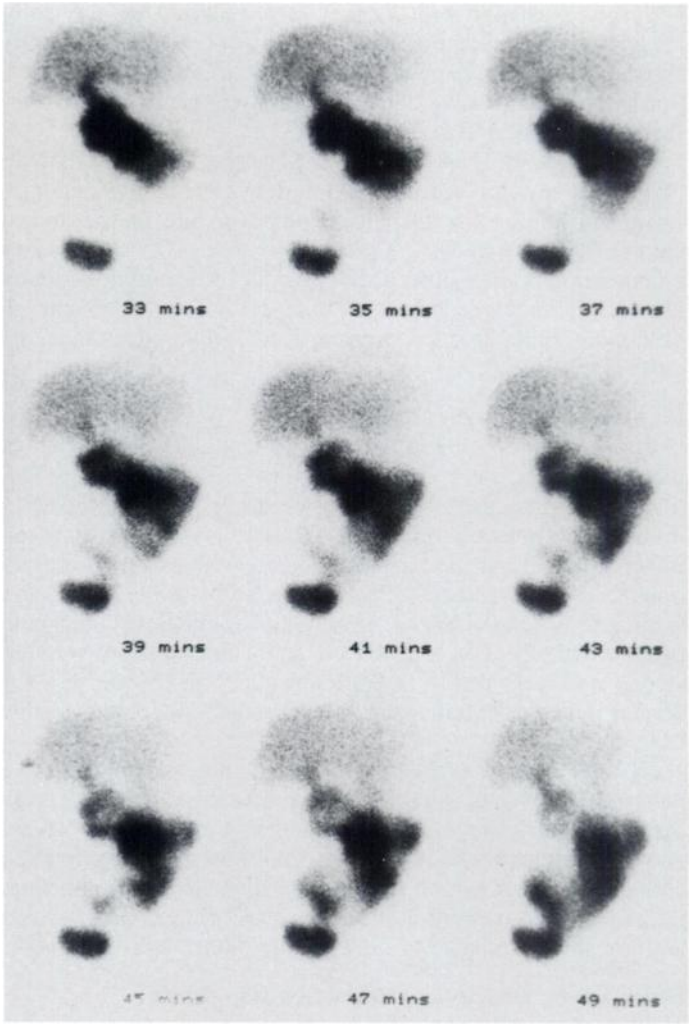

FIGURE 9. Postoperative hepatobiliary scan in a 3-mo-old infant 2 wk after Kasai portoenterostomy for biliary atresia. The scan reveals (images 33–50 min) good clearance from the parenchyma via the portoenterostomy into the small bowel. There is no holdup in the tracer at the anastomosis.

Hepatobiliary Scan Findings. Poor tracer extraction by the liver, reflecting severe hepatocellular dysfunction, has been described in these patients (*38*).

Byler Disease

Byler disease is a rare disorder of bile acid excretion that causes severe intrahepatic cholestasis and progressive hepatocellular dysfunction (*3*).

Hepatobiliary Scan Findings. One child studied by our unit showed extremely poor extraction of tracer by the liver on initial examination at 1 mo of age. However, after partial diversion of the bile from entering the gut, there was improvement but still reduced tracer extraction and biliary excretion was seen in the gut and diversion.

POSTOPERATIVE HEPATOBILIARY SCINTIGRAPHY

Scintigraphy is useful in the postoperative assessment in infants who have had surgery on the biliary tree. After successful portoenterostomy for biliary atresia or surgery for repair of a choledochal cyst, scintigraphy will show patency of biliary excretion and whether the main route of bile excretion is to the gut or to an exterior bile diversion. Hepatobiliary scan findings are also used in assessment after liver transplantation.The main indications for performing scintigraphy are to assess hepatic perfusion, detect bile leaks and assess transit of radiopharmaceuticals from the liver into the small bowel (*8,9*).

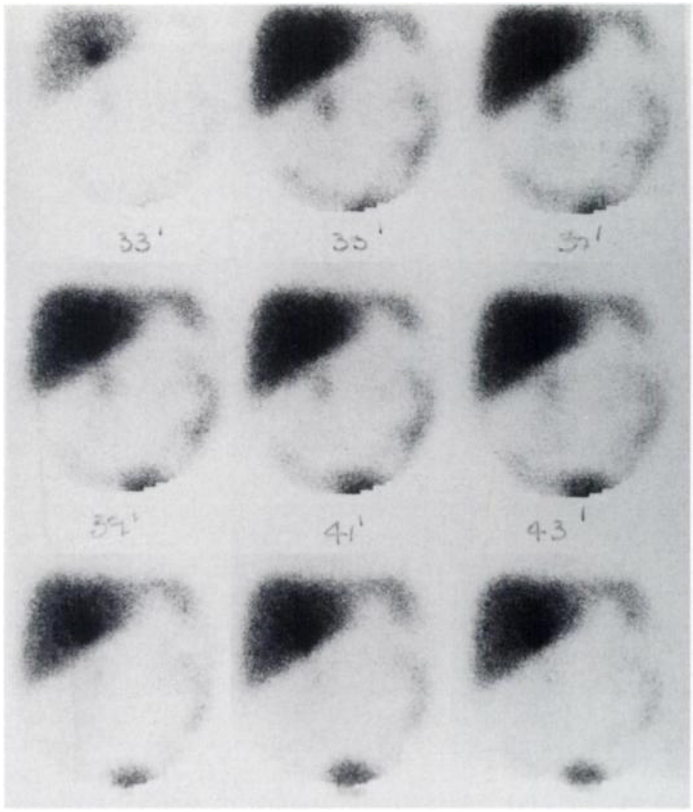

FIGURE 10. Bile leak complication 3 days after portoenterostomy in an 11-wk-old infant with biliary atresia. The SPECT scan of the abdomen shows a focal collection of tracer at the anastomosis of bowel to liver and a diffuse increase of tracer throughout the peritoneal cavity confirming a bile leak.

Hepatobiliary Scan Findings

In patients with biliary atresia who have had a portoenterostomy, there is good extraction of tracer by the liver with prompt excretion into the surgical diversion (Fig. 9). Figure 10 shows a bile leak. There is usually good extraction of tracer by the liver; however, tracer is seen to accumulate in the peritoneal cavity (Fig. 10) or a localized bile collection. Obstruction may occur after liver transplantation or post-portoenterostomy. There usually is good extraction of tracer by the liver but poor or no excretion of tracer is seen into the gastrointestinal tract. Cholangitis is a common complication after portoenterostomy for biliary atresia. There is moderately good extraction of tracer by the liver; however, there usually is a delay in excretion. There may be irregular distribution of tracer with focal areas of holdup in the intrahepatic bile ducts. Parenchymal irregularity with photopenic areas may be seen if there is complicating hepatic abscess formation (*17,39,40*).

CONCLUSION

Hepatobiliary scintigraphy should be used as part of the overall evaluation of neonates and infants with neonatal cholestasis and jaundice. The early application of hepatobiliary scan findings in conjunction with other imaging modalities (e.g., ultrasound) will give an accurate indication of the cause of cholestasis in the majority of cases.

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