# Hepatobiliary Scintigraphy in Children with Cystic Fibrosis and Liver Disease

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Intra- and extrahepatic impairment of biliary drainage is important in the pathogenesis of liver disease in cystic fibrosis. Distal common bile duct obstruction is reported to occur in 13% to 96% of these patients. Between 1975 and 1993, 17 of 372 children (4.5%) with cystic fibrosis attending The Children's Memorial Medical Center in Chicago had liver disease based on clinical and laboratory findings. **Methods:** Hepatobiliary scintigraphy (HBS) with $^{99m}$Tc-DISIDA was performed on 12 of the 17 children (mean age at the time of exam was 9 yr, with a range of 1 mo to 21 yr). **Results:** All had hepatomegaly, four had splenomegaly and two had bleeding esophageal varices. Twenty HBS exams on these 12 patients documented nonvisualization of the gallbladder in 7, dilated intrahepatic ducts in 6 (only the left lobe was involved in 3 patients), nonvisualization of bowel in two, delayed peaking time in the liver (>10 min) in four patients, and delayed clearance from the liver parenchyma ($T_{1/2}$ > 20 min) in 11. There appears to be a spectrum of abnormal HBS findings in cystic fibrosis patients with liver disease. These are delayed clearance of liver parenchyma, nonvisualization of the gallbladder and dilated intrahepatic ducts with a predilection for the left lobe of the liver. These abnormal findings fluctuate in time and may not correlate with the findings on ultrasonography. **Conclusion:** Quantitative hepatobiliary scintigraphy is a valuable tool in the evaluation and management of the liver disease in this patient population.

**Key Words:** hepatobiliary scintigraphy; $^{99m}$Tc-DISIDA; cystic fibrosis

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Significant liver involvement occurs in 2%–5% of cystic fibrosis (CF) patients (*1*) and may present with hepatomegaly, jaundice or elevation of serum liver enzymes. Obstruction of the common bile duct is suggested to be the cause of liver involvement in these patients (*2*). We evaluated twelve symptomatic CF patients with hepatobiliary scintigraphy (HBS). Our findings corroborate a significant incidence of hepatobiliary disorders in CF and support the use of HBS in the diagnosis and management of such disorders.

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## METHODS

### Patients

Seventeen of 372 children (4.5%) with cystic fibrosis seen at the cystic fibrosis clinic of our institution over a period of 17 yr (November 1975/May 1993) had clinical evidence of liver disease and 12 (7 male, 5 female; age range: 1 mo–21 yr) were evaluated. These patients underwent a clinical examination, liver function tests, liver ultrasonography and HBS. Biochemical liver disease was defined as the presence of one or more of the following: serum alkaline phosphatase >200 U/liter, total serum bilirubin >1.2 mg/dl, gamma-glutamyl transpeptidase >40 U/liter, SGOT >35 U/liter, SGPT >44 U/liter. Hepatobiliary scintigraphy was performed after intravenous administration of 3.7 MBq/kg $^{99m}$Tc diisopropyliminodiacetic acid (DISIDA). Patients fasted for at least 2 hr prior to injection. Serial analog images were obtained every 5 min and 1-min digital computer images were obtained on a 64 × 64 matrix for 45 min. Delayed static images were obtained at varying intervals depending upon the clearance of the activity from the liver parenchyma. A region of interest was drawn over the right lobe of the liver and a time-activity curve of the liver was obtained. On this curve, the time to peak liver activity and the clearance half-time ($T_{1/2}$) of the liver were calculated. The analog images were analyzed for the time of gallbladder and bowel visualization and for a qualitative evaluation of the size of intra- and extrahepatic bile ducts.

## RESULTS

Twelve children with CF and liver disease based on clinical and laboratory findings were evaluated (Table 1). Two patients presented with liver disease before the diagnosis of CF was made. All patients studied scintigraphically had hepatomegaly and four had splenomegaly. All of them had biochemically documented liver disease and the serum bilirubin levels were above normal in three patients. Four patients had cirrhosis clinically (two of them with esophageal varices), two patients had fatty livers on liver biopsy, two patients had diabetes mellitus and abdominal pain, three patients had cholangitis and three had obstructive jaundice. Two patients had a history of meconium ileus. Twenty HBS studies were performed on the 12 patients, with follow-up exams on six patients. All patients except one (Patient 6) had one or more abnormal findings on the scintigraphic examination (Table 2). Two infants at the age of 1 mo and 4 mo had no activity in their bowel or gallbladders for 24 hr. One of them (Patient 1) had operative cholangiography and a "flush out" of sticky bile. She had a normal follow-up HBS 3.5 yr later. The other baby

**TABLE 1**
Clinical and Laboratory Findings on 12 Children with Cystic Fibrosis and Liver Disease

| Patient | | | Hepatobiliary Scintigraphy | | | | | Ultrasound | | | Labs | | | | | Clinical Data | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. | Name | Age | Gallbl | Liv p | Bow v | Liv $T_{1/2}$ | Ducts | Ducts | CNL | Spleen | AP | GGT | SGOT | SGPT | Bilirubin | HM | SM | |
| 1 | AC | 1 mo | nv | 15 | nv | slow | – | | | | | | | | | + | – | Obstructive jaundice |
| | | 3.5 yr | n | 8 | 5 | 17 | – | | | | 319 | 16 | 41 | 35 | 0.29 | | | |
| 2 | JM | 4 mo | nv | 10 | nv | slow | – | R | yes | n | 348 | 45 | 427 | 357 | 3.70 | + | – | Obstructive jaundice |
| | | 7 mo | 20 | 8 | 5 | 35 | – | | | | 228 | 33 | 97 | 26 | 0.25 | | | After UDCA therapy |
| 3 | KA | 3 yr | 45 | 15 | 45 | slow | – | n | yes | | | | | | | + | – | bx: fatty liver |
| 4 | MH | 5 yr | nv | 10 | 10 | 23 | L | n | yes | n | 466 | 81 | 258 | 226 | N | + | – | Cholangitis |
| 5 | DN | 6 yr | 5 | 5 | 5 | 15 | – | n | yes | large | 393 | 62 | 84 | 91 | 1.10 | + | + | bx: cholangitis |
| | | 7 yr | 10 | 7 | 15 | 15 | L | n | | | | | | | | | | |
| | | 9 yr | 5 | 5 | 60 | 20 | L | | | | | | | | | | | |
| 6 | MR | 7 yr | 10 | 5 | 15 | 30 | – | | | | 43 | | 52 | 25 | 0.40 | + | – | bx: fatty liver |
| 7 | DG | 8 yr | n | | | 180 | | n | | n | 385 | 271 | 129 | 130 | | + | – | bx: fatty liver, cirrhosis |
| | | 10 yr | n | | | 33 | | | yes | | | | | | | | | |
| 8 | KB | 10 yr | nv | 7 | 10 | 40 | L | n | yes | n | 40 | 49 | 187 | 74 | 0.40 | + | + | Cirrhosis, coll scan: nodular |
| | | 12 yr | nv | 5 | 5 | 18 | L | | | | | | | | | | | |
| 9 | HP | 14 yr | nv | 10 | 30 | slow | R,L | | | | 69 | | 97 | 55 | 0.40 | + | + | Cirrhosis, HSM, varices |
| 10 | LS | 14 yr | nv | 5 | 15 | 45 | R,L | | | | 413 | 121 | 80 | 98 | 0.40 | + | – | DM, cholangitis |
| | | 16 yr | nv | 30 | 120 | slow | – | n | yes | n | 413 | 121 | 80 | 98 | 0.40 | | | CBD obs, gallstone, bx: biliary fibrosis |
| | | 17 yr | nv | 6 | 20 | 30 | R,L | n | yes | n | | | | | | | | |
| 11 | BR | 17 yr | 25 | 7 | 15 | 30 | R,L | n | | | 23 | 198 | 42 | 43 | n | + | – | DM, abdominal pain |
| 12 | AH | 21 yr | nv | 20 | 30 | 23 | R,L | n | yes | large | 467 | | 163 | 102 | 2.20 | + | + | Cirrhosis, varices, bleeding |

gallbl = gallbladder; nv = not visualized; n = normal; liv p = liver peaking time (min); bow v = bowel visualization time (min); R = right; L = left; CNL = coarsely nodular liver; AP = alkalene phosphatase; GGT = gamma glutamyl transaminase; SGOT = serum glutamate oxalate transaminase; SGPT = serum glutamate piruvate transaminase; bil = bilirubin; HM = hepatomegaly; SM = splenomegaly; UDCA = ursodeoxycholic acid; bx = biopsy; coll scan = liver scintigraphy with sulfur colloid; HSM = hepatosplenomegaly; DM = diabetes mellitus; CBD obs = common bile duct obstruction; bil = biliary.

Normal values. Liver peaking time < 19 min, liver $T_{1/2}$ < 44 min (*10*), serum alkaline phosphatase <200 U/liter, gamma-glutamyl transpeptidase <40 U/liter, SGOT <35 U/liter, SGPT <44 U/liter, total serum bilirubin <1.2 mg/dl.

(Patient 2) was treated with ursodeoxycholic acid (UDCA) and a follow-up study demonstrated a return to normal 3 mo later (Fig. 1A and B). The patient had evidence of debris in the gallbladder and common bile duct on ultrasound with no intrahepatic ductal dilatation (Fig. 1C). The gallbladders of five other patients (Patients 4, 8, 9, 10 and 12) were not visualized, and two (Patients 9 and 10) had poor liver clearance (liver $T_{1/2}$ >60 min). In the remaining five patients (Patients 3, 5, 6, 7 and 11), the gallbladder was visualized within 45 min after injection. However, the clearance of activity from the liver was delayed in two (Patients 3 and 7) ($T_{1/2}$ >3 hr). Areas of retained activity were noted in the livers of six patients, suggesting dilatation of intrahepatic bile ducts; only the left lobe was involved in three of them (Fig. 2A–E).

Follow-up studies on three patients (Patients 7, 8 and 10) showed improvement in liver clearance over a period of 1 or 2 yr. Another patient (Patient 5) with normal quantitative parameters developed dilated intrahepatic ducts on follow-up studies.

Ultrasonography was performed in seven patients. All of them showed increased echogenicity of the liver (Fig. 1C), however, no ductal dilatations were observed. Patient 10 developed gallstones at 15 yr of age.

**TABLE 2**
Abnormal Scintigraphic Findings on 12 Patients with Cystic Fibrosis and Liver Disease

| Finding | Number of patients |
|---|---|
| Nonvisualization of gallbladder | 7 (no bowel activity at 24 hr in 2) |
| Delayed clearance of liver activity | 6 (despite normal gallbladder and bowel visualization in 2) |
| Dilated bile ducts | 6 (only left lobe involvement in 3) |

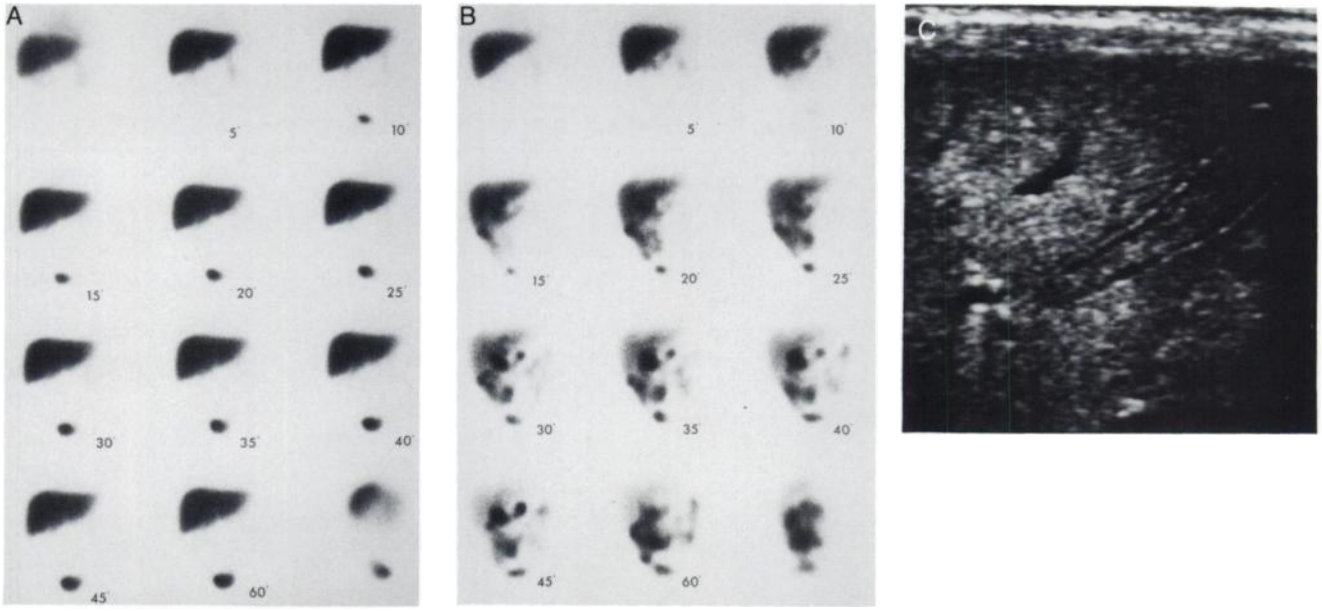


**FIGURE 1.** (A) Hepatobiliary scintigraphy performed on a 4-mo-old infant (Patient 2 in Table 1) with obstructive jaundice shows no activity in the gallbladder or in the intestine resembling the pattern seen in biliary atresia. (B) After 3 mo of medical therapy with ursodeoxycholic acid, a follow-up hepatobiliary scintigraphy shows normal flow of bile into the gallbladder and intestine. (C) Ultrasound shows inspissated bile in the gallbladder of Patient 2 (corresponds to A).

## DISCUSSION

There is a spectrum of abnormal findings on HBS performed on CF patients with liver disease. Gaskin et al. (*2*) reported that 96% of CF patients with liver disease had distal common bile duct obstruction. Nagel et al. (*3*) only found this in 13% of adults and considered intrahepatic impairment of biliary drainage to be important in the pathogenesis of liver disease. Among our group of twelve patients, only one had completely normal HBS (Patient 6). This patient had hepatomegaly and a fatty liver on biopsy. The bilirubin level was normal and SGOT was slightly elevated (52 U/l).

Two infants with hyperbilirubinemia and elevated liver enzymes had nonvisualization of the gallbladder and bowel, with very delayed liver clearance. It has been reported by several authors that cystic fibrosis may present in the newborn as a conjugated hyperbilirubinemia resembling neonatal hepatitis or biliary atresia (*4–6*). Patient 1 was treated by operative cholangiogram with flushing out of inspissated bile; her HBS at 3.5 yr showed visualization of the gallbladder and normal function. One of our infant patients (Patient 2) with no activity in the gallbladder or bowel was treated with UDCA with gradual return to a normal clinical state and a repeat HBS 3 mo later was normal, indicating patency of the obstructed intra- and/or extrahepatic bile ducts, with the resolution of a bile plug or inspissations by medical treatment. Another patient (Patient 10), who presented with diabetes and hepatomegaly developed biliary colic with obstructive jaundice and was treated with UDCA and showed improvement on HBS 1 yr later. Colombo et al. (*7*) reported improvement in hepatobiliary excretory function (appearance of bowel activity decreasing from 37 to 19 min, and liver $T_{1/2}$ from 35 to 26 min) following a 1-yr UDCA treatment, and Salh et al. (*8*) reported dissolution of gallstones in two adult CF patients. This improvement in biliary drainage is believed to be the result of UDCA-induced choleresis, by absorption and rapid resecretion of unconjugated UDCA from the biliary tree (*9*).

The gallbladders of five patients were not visualized despite the appearance of bowel activity, but two of them had very slow liver clearance, indicating intrahepatic stasis (Patients 9 and 10). Two patients with normal gallbladder visualization (Patients 3 and 7) had very slow liver clearance, and both patients had fatty livers on biopsy. The delayed liver clearance in these four patients (25%) with or without gallbladder visualization and evidence of bile flow into the intestine suggests intrahepatic cholestasis rather than a distal common bile duct obstruction. In this respect, our findings are in agreement with those of Nagel et al. (*3*) who reported the incidence of intrahepatic delay in excretion among their patients to be 22% (6/20).

Six patients had dilated intrahepatic ducts only in the left lobe in three. The intrahepatic prominence of the ductal system may be a result of repetitive intra- and/or extrahepatic biliary tract obstructions with bile stasis in the intrahepatic ducts. However, we cannot explain the preferential left lobe involvement, which has not been reported previously. Two of these patients (Patients 5 and 11) had otherwise normal HBS and one of them had cholangitis on biopsy.

There was a striking association between nonvisualization of the gallbladder, delayed excretion from the liver (predominantly left lobe) and a nodular liver on ultrasound

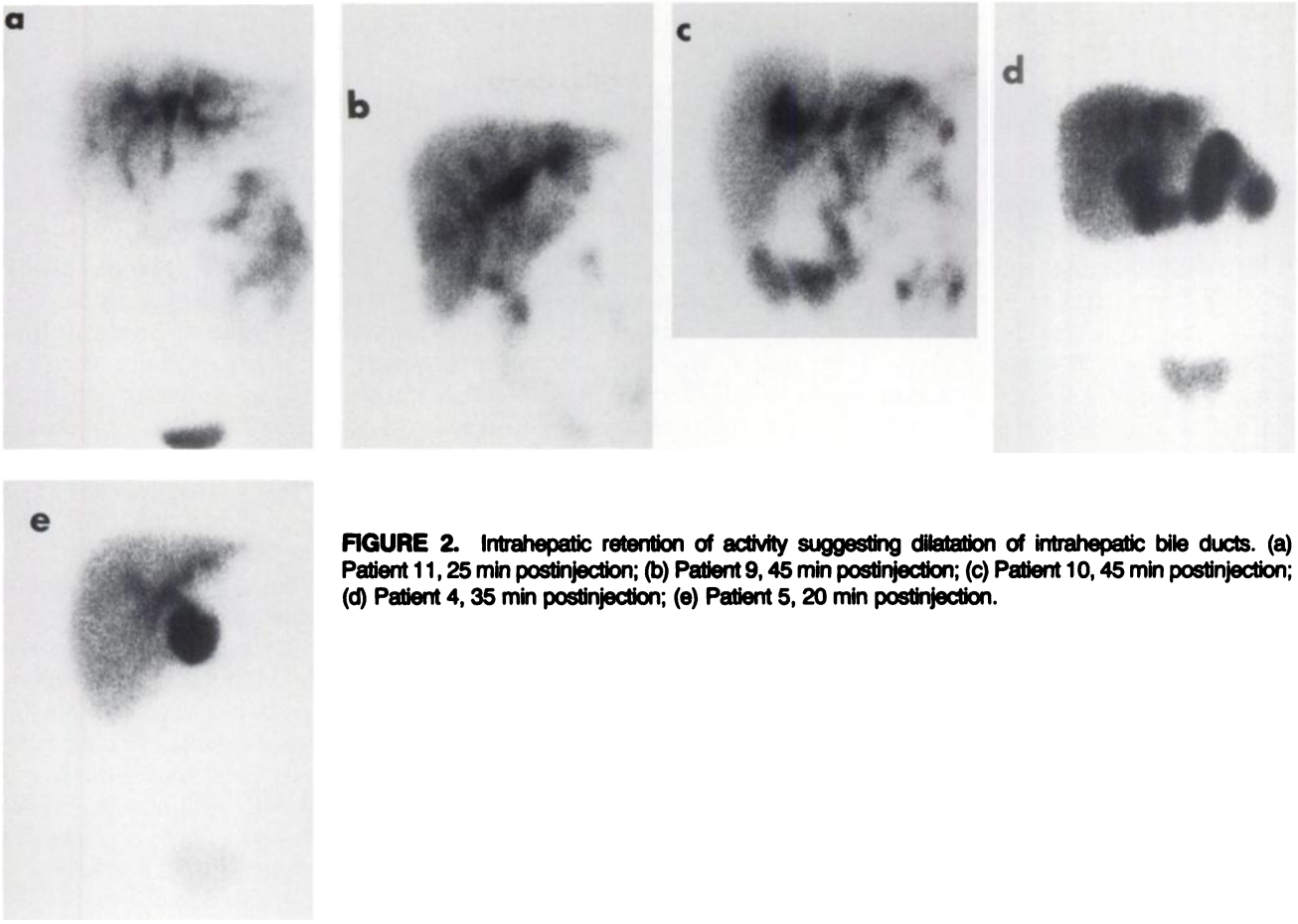


**FIGURE 2.** Intrahepatic retention of activity suggesting dilatation of intrahepatic bile ducts. (a) Patient 11, 25 min postinjection; (b) Patient 9, 45 min postinjection; (c) Patient 10, 45 min postinjection; (d) Patient 4, 35 min postinjection; (e) Patient 5, 20 min postinjection.

(Patients 4, 8, 9, 10 and 12). In only two patients was the nonfunctioning gallbladder later shown to function (Patients 1 and 2) and these were infants who had active therapy (operative cholangiogram and UDCA). It seems possible that nonvisualization of the gallbladder may be one of the earliest manifestations of liver involvement in cystic fibrosis, perhaps related to inspissated bile in the cystic duct. Unless corrected early, this obstruction becomes irreversible and the nonfunctioning gallbladder may aggravate the steatorrhea and be associated with increasing cholangitis, biliary fibrosis and ultimately cirrhosis.

## CONCLUSION

The liver disease in patients with cystic fibrosis is multifactorial and the presentation varies with age, i.e., obstructive jaundice at newborn age, hepatomegaly during infancy or cirrhosis in adulthood. The course of liver disease in cystic fibrosis seems to be related to the biliary drainage system which manifests as various abnormal findings on HBS, and these abnormal findings seem to fluctuate in time, suggesting an intermittent or reversible nature of the liver involvement. Hepatobiliary scintigraphy may help to differentiate between intra- and extrahepatic biliary tract involvement in cystic fibrosis patients, and may contribute to management with medical therapy (UDCA) or surgery.

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