Biliary complications of cystic fibrosis

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Abstract

One hundred and four adult patients with cystic fibrosis were evaluated for the presence of liver disease as defined by abnormal liver function tests of six months' duration, histological evidence of fibrosis or cirrhosis, or the presence of portal hypertension, or both. Twenty patients fulfilled these criteria and were evaluated further for the presence of biliary tract abnormalities with biliary scintigraphy using ^{99}Tc diisopropylphenyl-carboxymethyl iminodiacetic acid (DISIDA) and endoscopic retrograde cholangiography. Clearance of ^{99}Tc DISIDA from the liver and biliary tree was diminished at 45 (E45) and 60 (E60) minutes in the patients with liver disease compared with those without liver disease; E45=37.8% and 65.8%, $p<0.01$; E60=48.2% and 77.5%, $p<0.01$ respectively. Serial analogue images of the extrahepatic biliary tree were consistent with common bile duct obstruction with retention of DISIDA and tapering of the common bile duct in seven of 18 patients with and two of 10 patients without liver disease. Endoscopic retrograde cholangiography showed changes consistent with sclerosing cholangitis, with beading and stricturing of the intrahepatic ducts in 12 of the 14 patients. In all 14 patients, including those in whom biliary scintigraphy had suggested obstruction, no abnormality of the common bile duct was identified. These results indicate that abnormalities of the bile ducts in patients with cystic fibrosis related liver disease are confined to the intrahepatic biliary tree and that common bile duct strictures do not contribute to either the progression or development of liver disease in these patients.

The improvement in prognosis for patients with cystic fibrosis in recent decades can be largely attributed to the major advances in the management of bronchopulmonary sepsis and malnutrition.¹⁻³ Many cystic fibrosis patients are currently surviving into the fourth decade, and with this improved survival it has been recognised that the prevalence of cystic fibrosis related liver disease increases with advancing years ranging from 0.5-8.0% in children to 5-20% in adults.⁴

The development of liver disease in cystic fibrosis has been attributed to the inspissation of tenacious secretions within small bile ductules, with the subsequent development of progressive cholestasis, focal periportal biliary fibrosis, and eventually multilobular biliary cirrhosis and portal hypertension.⁵⁻⁸ Strictures of the extrahepatic biliary tree have been suggested as a possible aetiological factor in the development of cystic fibrosis related liver disease in previous reports,⁹⁻¹¹ and in one study common bile duct

strictures were detected in over 90% of patients with hepatic dysfunction.¹² A subsequent study, however, highlighted the structural abnormalities within the intrahepatic biliary tree and showed a relatively low prevalence of common bile duct strictures in these patients.¹³

Since common bile duct strictures may be a factor in the development of liver disease in cystic fibrosis, surgical correction of which might prevent progression of the disease,¹² we have evaluated the intra- and extrahepatic biliary tree in a group of patients with cystic fibrosis related liver disease.

Methods

PATIENTS

One hundred and four patients attending the Adult Cystic Fibrosis Centre were prospectively evaluated between June 1988 and June 1990. The median age of the patients was 19.5 years (range 12-42 years). The presence of liver disease was defined on the basis of hepatomegaly (liver span in excess of 12 cm) and splenomegaly (a palpably enlarged spleen), or both, confirmed by abdominal ultrasound, or abnormal liver biochemistry (bilirubin $>17\text{ }\mu\text{mol/l}$, alkaline phosphatase $>110\text{ iu/l}$, α glutamyl transferase $>50\text{ iu/l}$, 5-nucleotidase $>15\text{ iu/l}$, aspartate transaminase $>40\text{ iu/l}$) of at least six months' duration. On the basis of these criteria, 23 patients had liver disease. Three of these died during the study period before further hepatobiliary assessment. The remaining 20 patients were evaluated where possible with upper gastrointestinal endoscopy, abdominal ultrasound, biliary scintigraphy, and endoscopic retrograde cholangiography. Synthetic hepatic function was assessed with prothrombin time and serum albumin concentration. Hepatic histology was obtained in 14 patients by percutaneous liver biopsy (nine patients), peroperative liver biopsy (three patients), and at necropsy (one patient). The 20 patients with liver disease were comparable to the 84 patients without liver disease with regard to their clinical and nutritional status but had significantly less severe pulmonary disease as determined by standard pulmonary function tests and the number of days they had been admitted to hospital for pulmonary sepsis during the three year observation period (Table I).

ULTRASOUND

After an eight hour fast the 104 patients (20 patients with liver disease and 84 patients without liver disease) were scanned using real time ultrasound (ATL Mark 3) in the supine and the oblique positions. The biliary tree was assessed for the presence of cholelithiasis or intra- or

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TABLE I Nutritional and pulmonary features of patients with cystic fibrosis with and without liver disease (values, mean SEM)

	Liver disease (n=20)	No liver disease (n=84)
Age, median (yrs)	18	19.5
Male:female ratio	11:9	46:38
Pancreatic supplements (no (%))	18 (90%)	76 (90%)
Body weight (% IBW)	87.2	83.7
Hospitalisation for respiratory sepsis (days/2 yrs)	10	37*
FVC (% predicted)	85.9 (7.0)	67.9 (4.0)*
FEV ₁ (% predicted)	75.0 (7.0)	50.5 (4.0)*
PEFR (% predicted)	79.8 (7.0)	71.5 (4.0)

*p<0.05.
IBW=ideal body weight.

extrahepatic bile duct dilatation. A common bile duct diameter of less than 6 mm was considered normal.

BILIARY SCINTIGRAPHY

Hepatobiliary scintigraphy using ⁹⁹Tc diisopropylphenyl-carboxymethyl iminodiacetic acid (DISIDA) was performed on 28 patients with cystic fibrosis, 18 with liver disease, and 10 patients without liver disease. Parental permission to perform hepatobiliary scintigraphy was refused in two patients with liver disease. The 18 patients with liver disease were comparable with regard to age, sex, and nutritional status with the 10 patients without liver disease. After a four hour fast, 150 MBq of ⁹⁹Tc DISIDA was administered intravenously. A gamma camera interfaced to a dedicated computer was used to record data. Data were stored for 60 minutes at a frame interval of 1 per minute. At the end of the acquisition period a time/activity curve was generated for each patient using a region of interest over the liver and biliary tree, excluding the gall bladder. From the time/activity curve three parameters were derived – Tmax (time in minutes from injection of isotope to maximal hepatic activity), E45 and E60 (percentage clearance of DISIDA from the liver and biliary tree compared with the maximal activity, at 45 and 60 minutes respectively). The results were expressed as mean (SEM). The Wilcoxon rank sum test was used for statistical analysis.

Serial analogue images of the liver and biliary tree were obtained at two minute intervals for 60 minutes. The clearance of DISIDA at 60 minutes was qualitatively assessed by an observer (who was unaware of the clinical status of the patients) and defined as good, moderate, or poor. Similarly, the appearance of common bile duct tapering was described as present, absent, or doubtful. The results were analysed using χ^2 analysis.

ENDOSCOPIC RETROGRADE CHOLANGIOGRAPHY

Endoscopic cholangiography was attempted in 18 patients with liver disease using an Olympus T20 side viewing duodenoscope. The remaining two patients with liver disease refused permission for the procedure. Selective cannulation and imaging of the biliary tree was obtained in 14 patients. The duodenoscope was removed before obtaining anteroposterior, semiprone, and

oblique views of the biliary tree. Eleven patients were examined under local anaesthesia using sedation with midazolam or diazepam and three patients were examined under general anaesthesia with halothane and nitrous oxide. All patients received hyoscine butylbromide.

Results

PATIENTS

The biochemical, histological, and endoscopic characteristics of the 20 patients with cystic fibrosis related liver disease are shown in Table II. The median age of the patients was 18 years (range, 12–40 years). Liver biochemistry showed a predominant increase in the biliary canalicular enzymes with minor increases in the serum transaminase activities only. The biochemical values presented in Table II represent the determinations on entry to the study and these did not vary significantly on repeated three monthly analysis over the study period. Evidence of advanced liver disease as determined by the presence of portal hypertension or histological features of fibrosis or cirrhosis, or both, was present in 17 of the 20 patients (85%). The remaining three patients had persistently raised canalicular enzymes (alkaline phosphatase, α glutamyl transferase, and 5-nucleotidase, patients 6 and 8; alkaline phosphatase and 5-nucleotidase, patient 7) in the absence of a viral infection, drug toxicity, or a history of alcohol ingestion.

Six of the nine patients with oesophageal varices have had a haemodynamically severe oesophageal variceal haemorrhage. All patients were initially treated with injection sclerotherapy and in four resolution of the varices was achieved within four treatment sessions; the remaining two patients required portosystemic shunt surgery because of persistent variceal haemorrhage. There were no features of hepatic decompensation in any of the patients, although two developed ascites in relation to a variceal haemorrhage. Three patients complained of recurrent abdominal pain; common bile duct

TABLE II Clinical, biochemical, and histological features of patients with cystic fibrosis related liver disease

Patient No	ALP	α GT	SNT	PTR	Histology	PHT(S/V)
1	486	289	47	1.4	MBC	S+V
2	204	70	37	1.1	FBF	S
3	553	459	71	1.3	MBC	S+V
4	328	266	45	1.0	FBF	–
5	296	51	86	1.4	FC	S+V
6	399	169	22	1.2	N	–
7	260	46	21	1.1	–	–
8	188	104	22	0.9	N	–
9	194	73	23	1.0	FBF	–
10	191	406	26	0.9	MBC	S
11	389	124	35	1.2	FBF	S+V
12	218	33	16	1.1	FBF	V
13	497	175	104	1.3	–	S+V
14	130	42	10	1.1	FC	S
15	436	47	12	1.1	FBF	S
16	425	41	18	1.2	FBF	–
17	456	146	56	1.3	–	S+V
18	208	47	10	1.1	–	S+V
19	162	64	25	1.1	–	S+V
20	253	45	20	1.0	–	S

ALP=alkaline phosphatase; α GT= α glutamyl transferase; SNT=5 nucleotidase; PTR=prothrombin time ratio; MBC=multibobular biliary cirrhosis; FBF=focal biliary fibrosis; FC=fatty change; PHT=portal hypertension; S=spleen; V=varices.

calculi were present in two patients in both of whom endoscopic sphincterotomy and calculus extraction was performed. Endoscopic features of reflux oesophagitis were present in one patient.

ULTRASOUND

Abdominal ultrasound showed no abnormalities of the intra- or extrahepatic bile ducts in any patient. Gall bladder calculi were noted in four of the patients with liver disease (20%). In the remaining 84 patients without liver disease, gall bladder calculi were present in six patients (7%). These differences were not statistically significant using χ^2 analysis.

BILIARY SCINTIGRAPHY

⁹⁹Tc DISIDA biliary scintigraphy was performed in 28 patients, 18 with liver disease and 10 without liver disease. In the two patients with common bile duct calculi, biliary scintigraphy was performed after endoscopic cholangiography, sphincterotomy, and calculus extraction.

Hepatic uptake of DISIDA was delayed in the patients with liver disease, the Tmax in these patients was mean (SEM) 15.6 (2.1) minutes compared with 9.0 (0.5) minutes in the patients without liver disease ($p=0.01$) (Fig 1). There were also significant differences with regard to the percentage clearance of DISIDA from the liver and biliary tree at 45 and 60 minutes in the two patient groups. At 45 minutes, 37.8 (4.9)% of DISIDA had been cleared from the liver and biliary tree in the patients with liver disease compared with 65.8 (4.6)% in those without liver disease ($p<0.01$). Similarly, at 60 minutes 48.2 (5.0)% and 77.5 (2.9)% of DISIDA was cleared from the liver in the patients with and without liver disease respectively ($p<0.01$) (Fig 1). Serial analogue images showed retention of DISIDA within the common bile duct in 45% of the patients with liver disease and 20% of the patients without liver disease. Similarly, apparent tapering of the common bile duct was shown in seven

Figure 1: Maximum time (Tmax) for hepatic uptake of ⁹⁹Tc DISIDA and percentage clearance of ⁹⁹Tc DISIDA from the liver and biliary tree at 45 (E45) and 60 (E60) minutes.

TABLE III Evaluation of the extrahepatic biliary tree using biliary scintigraphy in patients with cystic fibrosis with and without liver disease

	Liver disease (n=18) (no (%))	No liver disease (n=10) (n (%))
CBD clearance of ⁹⁹ Tc DISIDA:		
Good	4 (22)	5 (50)
Moderate	6 (33)	3 (30)
Poor	8 (45)	2 (20)
Tapering of CBD:		
Present	7 (39)	2 (20)
Doubtful	3 (17)	3 (30)
Absent	8 (44)	5 (50)

CBD=common bile duct; DISIDA=diisopropylphenol-carboxymethyl iminodiacetic acid.

of 18 patients with liver disease (39%) and in two of 10 patients without liver disease (20%) (Table III). These differences were not statistically significant using χ^2 analysis.

ENDOSCOPIC RETROGRADE CHOLANGIOGRAPHY

Abnormalities of the intrahepatic ducts were noted in 12 of the 14 patients (85%). The changes varied from minor irregularity and tapering of the smaller intrahepatic biliary radicals to stricturing, beading, and segmental dilatation of the large bile ducts (Table IV). Strictures of the extrahepatic biliary tree were not observed. Two patients had common bile duct calculi, both of whom were symptomatic.

A discrepancy between the findings at endoscopic cholangiography and biliary scintigraphy was noted in patients who had undergone both examinations. In seven patients serial analogue images had been interpreted as indicating the presence of a common bile duct stricture on the basis of a tapering appearance and retention of isotope. Endoscopic cholangiography was performed in four of these patients and showed no evidence of a common bile duct stricture or retention of contrast within the biliary tree. An example of the discordant findings at cholangiography and scintigraphy is illustrated in Figure 2 which shows retention of DISIDA within the biliary tree and tapering of the common bile duct in a 15 year old girl with cirrhosis and portal hypertension in whom retrograde cholangiography showed a normal extrahepatic biliary tree.

Discussion

A prevalence of liver disease of 20% in an

TABLE IV Cholangiographic abnormalities in 14 patients with cystic fibrosis related liver disease

Patient no	Abnormality
1	Beading and stricturing of right and left IHDS
2	Normal
3	Beading and stricturing of right and left IHDS
4	Variation in calibre of left IHDS
5	Beading and stricturing of right and left IHDS
6	Variations in calibre of right and left IHDS
7	Minor variation in calibre of left IHD
8	Minor beading of right and left IHDS
9	Minor variations in calibre of right IHDS
10	Beading and stricturing of right and left IHDS
11	Normal
12	Variations in calibre of right IHD
13	Minor variations in calibre of left IHD
14	Stricturing of right and left IHDS

IHDS=intrahepatic duct system.

Figure 2: Biliary scintigraphy (left) and endoscopic retrograde cholangiography (right) in a 15 year old girl with cystic fibrosis related liver disease and portal hypertension. The retention of ^{99}Tc DISIDA and the tapering appearance of the common bile duct were suggestive of common bile duct obstruction which was excluded by the normal appearances of the common bile duct at endoscopic cholangiography. Feature consistent with sclerosing cholangitis are noted within the extrahepatic biliary tree.

adult population of cystic fibrosis patients in the present series is similar to that recently reported.¹³ Although most patients had advanced liver disease as reflected by the presence of fibrosis or cirrhosis and portal hypertension, hepatic synthetic function was well preserved and hepatic decompensation rare and seen only in relation to a variceal haemorrhage. Symptoms referable to the biliary tree were uncommon and observed only in patients with common bile duct calculi. None of the patients had symptoms of ascending cholangitis or cholestasis. The patients with liver disease had significantly less severe bronchopulmonary disease, an observation previously reported and consistent with the presence of multiple mutations at the cystic fibrosis gene locus giving rise to different phenotypic expressions of the disease.¹⁴

The presence of cystic fibrosis related liver disease has been historically ascribed to obstruction of the intrahepatic bile ductules with inspissated mucus, with the development of progressive cholestasis, periportal fibrosis, and multilobular biliary cirrhosis.⁶⁻⁸ More recently, abnormalities of the larger intrahepatic bile ducts in cystic fibrosis related liver disease have been highlighted and suggested as important factors in determining the development or progression of the disease.¹³ Features consistent with sclerosing cholangitis have been reported in four of 102 patients with cystic fibrosis, although two of these had coexistent inflammatory bowel disease.¹⁵ Recent reports have highlighted

abnormalities of the intrahepatic biliary tree with cholangiographic features of sclerosing cholangitis in patients with cystic fibrosis related liver disease which were an invariable finding in some but not all studies.^{12,13} Cholangiographic features of sclerosing cholangitis of varying severity confined to the intrahepatic biliary tree were observed in most patients with cystic fibrosis related liver disease in the present series. The findings on biliary scintigraphy would be in keeping with the presence of an intrahepatic duct process such as sclerosing cholangitis with heterogeneous retention of DISIDA and significant delays in isotope clearance at 45 and 60 minutes. Although the uptake of DISIDA was slower in the patients with liver disease compared with those without liver disease, this difference was small, indicating relatively well preserved hepatic parenchymal function in patients with cystic fibrosis related liver disease.

Recent studies have indicated that strictures of the extrahepatic biliary tree are common in patients with cystic fibrosis and liver disease. Using biliary scintigraphy, percutaneous cholecystography, and transhepatic cholangio-

graphy, common bile duct strictures were shown in over 90% of patients with cystic fibrosis related liver disease and it was postulated that common bile duct strictures might contribute to the development or progression, or both, of liver disease in these patients.¹² However, in a subsequent study of a cohort of patients with cystic fibrosis related liver disease investigated with endoscopic retrograde cholangiography, common bile duct strictures were found in only 13%.¹³ It was argued that the discrepancy in these results was related to the fact that in the latter series the patients were not prospectively evaluated, many may have been malnourished, and the cholangiographic technique used may have underestimated the prevalence of common bile duct strictures.¹⁶ These arguments cannot, however, be used to explain the observation in the present series that common bile duct strictures were not identified since the patients were prospectively evaluated at six monthly intervals over a three year period, almost all had advanced liver disease, and most were maintained on pancreatic supplements with a nutritional status comparable with an age matched group of patients without liver disease. Furthermore, the cholangiographic technique used permitted optimal visualisation of the extrahepatic biliary tree. It is possible that the high prevalence of common bile duct strictures previously reported relates to the inclusion of a significant number of patients with recurrent abdominal pain of biliary tract origin many of whom underwent surgery with complete relief of symptoms and improvement in hepatic function.¹² In contrast, in the present series only three of the patients complained of recurrent abdominal pain, and this was attributable to common bile duct calculi in two patients and peptic ulcer disease in the remaining patient, the symptoms of which resolved after appropriate treatment in all.

In previous studies using serial analogue images of the biliary tree after intravenous administration of DISIDA, retention of the radiolabelled tracer in the extrahepatic biliary tree had been interpreted as indicating the presence of distal common bile duct obstruction.¹² However, as illustrated by our findings, retention of DISIDA within the extrahepatic biliary tree can occur in the absence of cholangiographically evident common bile duct obstruction. Thus, in four of the patients in whom biliary scintigraphy suggested extrahepatic biliary obstruction, cholangiographic findings showed common bile ducts of normal calibre without stricture formation and free flow of contrast into the duodenum. Moreover, in the two patients with common bile duct stones who had undergone sphincterotomy and stone extraction, the biliary scintigraphic findings suggested common bile duct obstruction. Finally, in a significant number of the patients without liver disease, the scintigraphic findings were consistent with extrahepatic duct obstruction. These observations indicate that while biliary scintigraphy may be a valuable diagnostic procedure

in establishing common bile duct obstruction in most situations, its value in this regard in patients with cystic fibrosis is questionable. It is possible that factors other than mechanical obstruction are responsible for the retention of radioisotope. Thus, biliary hypomotility and stasis or adherence of DISIDA to abnormally viscid mucus within the biliary tree, or both, could result in prolonged retention and mimic mechanical obstruction.

The results of the present study clearly show that extrahepatic biliary strictures are not a prevalent finding or a factor in the pathogenesis or progression of liver disease in patients with cystic fibrosis. Common bile duct strictures may be more prevalent in patients with cystic fibrosis related liver disease who have recurrent abdominal pain in the absence of biliary calculi, pancreatitis, peptic ulcer disease, and meconium ileus equivalent, who should be investigated further with endoscopic retrograde cholangiography or percutaneous transhepatic cholangiography. Cholangiographic features of sclerosing cholangitis are an almost universal finding in patients with cystic fibrosis related liver disease and this process, rather than common bile duct stricture is likely to be a major factor in the development and progression of cystic fibrosis related liver disease.

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