Hepatobiliary complications in chronic pancreatitis

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SUMMARY Thirty nine patients undergoing surgery for chronic pancreatitis were investigated for evidence of hepatobiliary disease. In addition to pre-operative assessment by liver function tests, ultrasound, ERCP (in 33) and percutaneous transhepatic cholangiography (in five), all had peroperative liver biopsy. Common bile duct stenosis was diagnosed in 16 (62%) of the 26 patients with successful cholangiography. Features of extrahepatic biliary obstruction were found on biopsy in 11 patients, three of whom showed features of secondary sclerosing cholangitis. No patients had secondary biliary cirrhosis. Three had parenchymal liver disease (cirrhosis, resolving hepatitis and alcoholic hepatitis respectively) and two others had features suggestive of previous alcohol-induced injury. Five (83%) of the patients with clinical jaundice had biopsy features of extrahepatic biliary obstruction, as did eight (67%) with alkaline phosphatase above twice normal and seven (44%) with radiological common bile duct stenosis. Neither alkaline phosphatase rise, nor common bile duct stenosis alone or in combination, were a reliable indication of the need for biliary enteric bypass surgery. Pre-operative liver biopsy may be a valuable adjunct in the assessment of such patients.

Chronic pancreatitis may give rise to, or be associated with, various hepatobiliary disorders. Stenosis of the intrapancreatic portion of the common bile duct may result in obstructive jaundice, a complication first recognised by Riedel in 1896¹ and later reported by Mayo Robson.² Jaundice is often transient after an exacerbation of chronic pancreatitis³ but may persist if there is fibrosis and scarring of the pancreatic tissue around the lower common bile duct. Lesser degrees of stenosis may produce no symptoms or signs but may be suggested by rises in serum alkaline phosphatase concentration.⁴ Little is known about the natural history of biliary obstruction in chronic pancreatitis. Cholangitis⁵ is probably rare in unoperated cases and although longer term obstruction may cause secondary biliary cirrhosis,^{5,6} this is also a rare complication.⁷

Differences in diagnostic criteria and patient selection make the incidence of common bile duct stenosis in chronic pancreatitis difficult to determine.^{3,6,8-10} The quoted operation rate for patients with stenosis also varies considerably from 3.7% in a large series of 1262 patients¹⁰ to 16% of a

series of 38 patients.¹¹ Ammann, in a longitudinal study of patients followed for up to 20 years (median 10.4 years), found that 22 (9%) of 245 patients required surgery for biliary obstruction.¹²

In the Western world alcohol is the commonest cause of chronic pancreatitis and liver cirrhosis. Cirrhosis is, however, usually an uncommon finding in patients with chronic pancreatitis.^{3,13} The reasons for this are uncertain but might be because alcohol-induced chronic pancreatitis is likely to be noticed earlier. Clark, however, found cirrhosis at autopsy in 17 (47%) of 36 patients with alcoholic pancreatitis¹⁴ while two recent prospective studies of chronic pancreatitis patients found alcoholic liver disease on biopsy in 30% and 40% of cases respectively.^{15,16} Alcoholic liver disease must, therefore, be considered in the assessment of patients with chronic pancreatitis who have deranged liver function,¹⁷ particularly if surgery is being contemplated. We have sought to investigate the association between hepatobiliary disease and chronic pancreatitis in patients under our care.

Methods

PATIENTS

Thirty nine consecutive patients undergoing surgery

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for chronic pancreatitis between 1 January 1984 and 31 January 1987 in Glasgow Royal Infirmary had peroperative liver biopsy performed. The patients comprised 32 men and seven women with a median age of 42 years (range 27–72). Chronic pancreatitis was considered secondary to alcohol abuse in 30 patients (77%), pancreas divisum in one and polyarteritis nodosa in one. No definite aetiological factor could be established in the remaining seven patients although one had gall stones at the time of diagnosis of chronic pancreatitis and one had hypercalcaemia although primary hyperparathyroidism was not confirmed. Eight patients (21%) had previously undergone pancreatic surgery but none had undergone a previous biliary enteric bypass. Five had previously undergone cholecystectomy. The indications for surgery during the index admission included obstructive jaundice in six patients and the presence of a cyst or pseudocyst in seven. In the remainder, pain, inadequately controlled by narcotic analgesics, was the predominant indication for surgery. The median duration of symptoms before surgery was 36 months, ranging from two weeks (in one patient with jaundice) to 14 years.

PRE-OPERATIVE ASSESSMENT

Pre-operative assessment in all patients included routine liver function tests and ultrasound scan of the pancreas, liver, and biliary tree. Radiology of the biliary tree was attempted pre-operatively in 38 of the 39 patients, at the time of ERCP in 33 and by percutaneous transhepatic cholangiogram (PTC) in

five. In those patients judged to have a common bile duct stenosis based on the presence of a persistent narrowing of a portion of the duct, this was categorised according to the classification of Caroli and Nora.¹⁸ Both type 1 stenosis (long retropancreatic stenosis) and type 3 stenosis ('hourglass type' narrowing of the mid common bile duct at the upper border of the pancreas) are considered characteristic of chronic pancreatitis (Fig. 1). Stricture at the sphincter of Oddi (type 2) is typical of ampullary lesions. Type 4 stenosis (medial or lateral compression with deviation of the common bile duct) may be associated with chronic pancreatitis, cyst or carcinoma, while the type 5 stenosis (complete occlusion of the duct at the upper border of the pancreas) is characteristic of pancreatic cancer. The cholangiograms were assessed by an independent radiologist (AH) unaware of the clinical details, and the stenosis length and maximum diameter of the duct above the stenosis were measured without correction for magnification.

SURGERY

Fourteen patients underwent formal pancreatic resection (distal pancreatectomy – nine, pancreaticoduodenectomy – two, and total pancreatectomy – three). Two of the patients undergoing distal pancreatectomy had the duct in the pancreatic remnant drained by pancreaticojejunostomy. Eight patients underwent longitudinal pancreaticojejunostomy. Three had a transduodenal sphincteroplasty with the removal of stones from the pancreatic duct¹⁹ and one patient with pancreas divisum had accessory duct sphincteroplasty. Five patients underwent cystogastrostomy, and one had needle aspiration of multiple cysts in the head of the pancreas. One patient had pancreatic biopsy alone. Six patients (15%) had a biliary enteric bypass done comprising cholecystjejunostomy in three (one with additional pancreaticojejunostomy), choledchojejunostomy in two (one with pancreaticojejunostomy and one with gastrojejunostomy) and choledochoduodenostomy in one.

LIVER HISTOLOGY

The liver biopsy was usually taken from the right lobe, using a Tru-Cut biopsy needle (Travenol Laboratories, Illinois, USA). The biopsies were processed by standard means and sections routinely stained with haematoxylin and eosin, Masson's trichrome, Gordon and Sweets' reticulin and PAS/diastase. Where appropriate Perls' iron stain and Shikata's orcein stain were carried out. The biopsies were examined by an independent pathologist (RMacS) unaware of the patients' clinical details.

Fig. 1 Diagram showing classification of bile duct stenoses according to Caroli and Nora.¹⁸ The type 1 stenosis (long retropancreatic stenosis) and type 3 stenosis ('hourglass-type' narrowing of mid common bile duct) are considered characteristic of chronic pancreatitis.

STATISTICAL ANALYSIS

Statistical analysis of the differences between groups of patients was performed by the Mann-Whitney U test.

Results

BIOCHEMISTRY

Six patients (15%) were clinically jaundiced before surgery (mean serum bilirubin concentration 156 $\mu\text{mol/l}$, normal range 3–22 $\mu\text{mol/l}$). Serum alkaline phosphatase concentration was raised in 19 patients (49%) with 12 (31%) having a rise greater than twice the upper limit of normal. Serum aspartate transaminase concentration was raised in 12 patients (31%) but in only three patients was the rise greater than twice normal. Alanine transaminase concentration was raised in 11 patients (28%), and in four patients this rise was greater than twice normal.

RADIOLOGY

Biliary radiology was obtained in 26 patients (67%), during ERCP in 21 patients and PTC in five. Sixteen of these 26 patients (62%) were considered to have stenosis of the lower common bile duct. Diameters of the bile duct above the stenosis in these 16 patients ranged from 7 to 25 mm (mean 15.5 mm) and the stenosis length varied from 10 to 70 mm (mean 36 mm). The remaining 10 patients all had normal biliary radiology with maximum duct diameters ranging from 5 to 15 mm (in a patient after cholecystectomy). The mean duct diameter in these patients was 8.6 mm and was significantly different from those with a stenosis ($p < 0.001$). Twelve patients were considered to have type 1 biliary stenosis and there was one case each of types 2, 3, 4, and 5.

HISTOLOGY

Twenty three liver biopsies were considered to show non-specific features; five of these had minimal fatty infiltration, increased lipofuscin deposition and nuclear polyploidy; 18 showed reactive changes of varying degree comprising Kupffer cell hyperplasia, increased numbers of intrasinusoidal mononuclear cells including occasional ceroid laden macrophages, and a mild, often focal infiltration of mononuclear cells in the portal tracts. In 11 patients the biopsy showed histological features consistent with biliary tract disease. In seven there was cholestasis with mild portal tract changes comprising oedema, cholangitis and increased prominence of marginal bile ducts. In one patient there was cholestasis and more severe portal tract changes comprising oedema, cholangitis, marginal duct proliferation, cholangiolitis and some portal fibrosis (Fig. 2). In three biopsies there were

features of a secondary sclerosing cholangitis (Fig. 3) with fibro-obliterative lesions affecting interlobular bile ducts; in all three biopsies there was portal fibrosis and in two there were superimposed features of an acute cholangitis with a moderately intense periductal and portal tract neutrophil polymorph infiltrate.

The remaining five patients comprised two cases of mild perivenular scarring (possibly residual to alcohol induced injury), one case each of alcoholic hepatitis, resolving acute hepatitis (possibly of drug or viral aetiology) and cirrhosis (possibly of alcohol aetiology in that there was a previous clinical history of alcohol abuse although the biopsy did not show features of a superimposed alcoholic hepatitis).

BIOCHEMICAL/RADIOLOGICAL/HISTOLOGICAL CORRELATIONS

All six jaundiced patients had bile duct stenosis, three with type 1 stenosis and one each with types 3, 4, and 5. Of the 26 patients with a pre-operative cholangiogram, 10 (71%) of the 14 patients with a raised serum alkaline phosphatase concentration (including all nine with a rise greater than twice normal) had bile duct stenosis. Alkaline phosphatase concentrations were also raised in four patients found radiologically to have a normal common bile duct. Nine (90%) of those with a raised aspartate transaminase concentration and eight (89%) of those with a rise in serum alanine transaminase concentration had bile duct stenosis demonstrated.

Seven (44%) of the 16 patients with common bile duct stenosis exhibited histological features of extrahepatic biliary obstruction (Table 1) as did five (83%) with clinical jaundice, eight (67%) with alkaline phosphatase rise greater than twice normal and six (67%) of the nine patients with both alkaline phosphatase rises greater than twice normal and common bile duct stenosis. The maximum common bile duct diameters were similar whether histological features of extrahepatic biliary obstruction were present or not (17 (4) mm ν 14 (6) mm) but the mean stenosis length was longer (44 (23) mm ν 29 (12) mm) the difference, however, failing to reach statistical significance. The sensitivities and specificities of each parameter for predicting the presence of extrahepatic obstruction on liver biopsy are shown in Table 2.

SURGERY

The presence of jaundice was the major indication for biliary enteric bypass and four of the six patients jaundiced pre-operatively underwent either biliary enteric bypass (in three) or pancreaticoduodenectomy (as pancreatic carcinoma could not be excluded) in one. All four patients had bile duct stenosis but only three had histological features of

Fig. 2 Liver biopsy showing well developed features of extrahepatic biliary obstruction; there is portal tract oedema and fibrosis, a mixed acute and chronic inflammatory cell infiltrate of the portal tract, increased prominence of marginal bile ducts and cholangioles and an acute cholangiolitis. (H & E)

extrahepatic obstruction on biopsy, the fourth having alcoholic hepatitis. The two remaining jaundiced patients did not have a biliary enteric bypass performed (see below).

Three other non-jaundiced patients with common bile duct stenosis and a raised alkaline phosphatase concentration pre-operatively also had a biliary enteric bypass carried out. Only one of these patients had histological feature of extrahepatic biliary obstruction on liver biopsy; one had cirrhosis and the other non-specific features.

OUTCOME

Three of the six patients having biliary enteric bypass had an uncomplicated postoperative recovery and none have since developed recurrent jaundice or cholangitis. Two patients undergoing cholecyst-jejunostomy developed recurrent jaundice at two months and two years postoperatively. Cholangio-

graphy in both patients showed a non-functioning biliary enteric anastomosis, one having developed biliary debris and the other gall stones in the common bile duct. Both have since undergone Roux-en-Y choledochojejunostomy and currently remain free of symptoms. The sixth patient demonstrated to have a type 5 biliary stenosis at the initial ERCP had a choledochoduodenostomy carried out but subsequently developed further pain and five months later underwent pancreaticojejunostomy. Biopsies of the pancreatic head had, on both occasions, shown chronic pancreatitis. He remained symptomatic and has since undergone pancreaticoduodenectomy when histology showed a small, unsuspected pancreatic carcinoma with surrounding pancreatitis.

Three of the other 10 patients with radiological bile duct stenosis were jaundiced; one underwent pancreaticoduodenectomy and remains well but two others who did not have biliary enteric bypass

Fig. 3 Liver biopsy showing features of sclerosing cholangitis; there is periductal fibrosis and inflammation with epithelial degeneration and partial obstruction of the duct lumen; there is portal tract fibrosis and periportal inflammation with ductular proliferation and an acute cholangiolitis. (H & E)

developed postoperative biliary complications. One developed a bile leak after cholecystectomy, transduodenal sphincteroplasty and exploration of the pancreatic duct. Leakage from the cystic duct stump was demonstrated by fistulography but this settled on conservative treatment. The other patient, an alcoholic, had presented late with advanced biliary obstruction and haemorrhage into a large pseudocyst. Liver function improved during a period of percutaneous biliary drainage. He underwent cystogastrostomy but without biliary-enteric bypass. His biliary obstruction was not relieved by drainage of the pseudocyst and he died one month later from liver failure. Of the remaining seven patients with common bile duct stenosis, two have had further pain and are to undergo pancreatic surgery, one has died of a myocardial infarction and four others remain well. None have had any symptoms related to the biliary tree.

Discussion

Common bile duct stenosis is a well recognised complication of chronic pancreatitis but its incidence, significance and natural history is uncertain. The present study was intended to address the first two issues by correlating the biochemical, radiological and histological sequelae of this complication in an unselected, consecutive group of patients undergoing surgery for chronic pancreatitis.

The incidence of common bile duct stenosis reported in the literature varies widely^{3, 6, 8-12} and is difficult to evaluate because of differences in patient selection and the diagnostic criteria used to define chronic pancreatitis and common bile duct stenosis. Radiological evidence of common bile duct stenosis was found by Sarles *et al* in 63% of a series of 100 patients with chronic calcifying pancreatitis.³ The lowest incidence of common bile duct

Table 1 Biochemical, histological and operative data on 16 patients with radiologically demonstrated common bile duct stenosis

Patient	Bilirubin ($\mu\text{mol/l}$)	Alkaline phosphatase (IU/l)	Liver histology	Operation
AD	175	680	EHO-severe	Cystogastrostomy
BG	155	2080	EHO/SSC	CCJ
JSw	185	670	EHO/SSC	Choledochoduodenostomy
CL	335	660	EHO	CCJ
TW	57	1470	EHO	TDS
WMcA	67	1100	Alc Hep	Pancreaticoduodenectomy
EMcC	26	4100	EHO	CCJ/PJJ
MH	11	680	Cirrhosis	CDJ/GJJ
MHy	10	1070	NSR	CDJ/PJJ
AA	23	380	Hepatitis	Distal pancreatectomy
JC	10	210	NSR	PJJ
JS	12	190	NSR	PJJ
LF	8	150	EHO	TDS
MM	11	245	NSR	TDS
RR	6	160	NSR	Cyst aspiration
RS	12	205	NSR	Cystogastrostomy

EHO – extrahepatic biliary obstruction, SSC – secondary sclerosing cholangitis, Alc Hep – alcoholic hepatitis, NSR – non-specific reactive changes, CCJ – cholecystjejunostomy, TDS – transduodenal sphincteroplasty, CDJ – choledochojunostomy, PJJ – pancreaticojejunostomy, GJJ – gastrojejunostomy. (Normal ranges – bilirubin $<22 \mu\text{mol/l}$, alkaline phosphatase $<280 \text{ IU/l}$.)

stenosis (4%) was reported from a large series of 1262 patients.¹⁰ These patients were not screened biochemically or radiologically for the presence of common bile duct stenosis and this figure represents the small proportion of patients with clinically apparent common bile duct obstruction; it undoubtedly underestimates the true incidence of common bile duct stenosis. Bile duct abnormalities are found more commonly in severe chronic pancreatitis, as assessed by ERCP, than in mild cases (69% v 28%)²⁰ and this may also account for the different incidence reported in various series.

The incidence of common bile duct stenosis in our 26 evaluable patients was high at 62% and almost identical to that reported by Sarles *et al.*³ All of our

patients had chronic pancreatitis of sufficient severity to warrant surgery and this may explain the high incidence of bile duct abnormality. Because 13 of our 39 patients did not have biliary radiology, however, this figure must be interpreted with caution. None of these 13 patients had been jaundiced, although five had alkaline phosphatase rises which, in three of them, exceeded twice the upper limit of normal. On liver biopsy three of these 13 patients showed features of extrahepatic obstruction. This suggests that the total number of patients with common bile duct stenosis in this series may have been between 19 (49%) and 21 (54%) of the total group of 39 patients, and could be higher. Therefore, at least half the patients coming to surgery for chronic pancreatitis may have some degree of biliary obstruction with important implications for treatment. Although the patterns of bile duct abnormality in association with chronic pancreatitis and other pancreatic diseases have been carefully documented^{18,20} the criteria for determining the presence of common bile duct stenosis appear imprecise. The type 1 stenosis is most frequently encountered in chronic pancreatitis but it need not be associated with any dilatation of the proximal biliary tree. Although there should be no dispute about severe obstruction, minimal change in the calibre of the bile ducts may be difficult to evaluate and label correctly, particularly if the radiological assessment has depended on the relatively poor quality radiograms obtained at cholecystography or intravenous cholangiography. Evaluation of the biliary tree for stenosis should be based on cholangiograms obtained by ERCP or PTC. Furthermore, stenosis might be more accurately defined if

Table 2 Analysis of parameters predicting the presence of extrahepatic biliary obstruction on liver biopsy

Parameter	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Correct
Jaundice	45%	96%	83%	82%	82%
Alkaline phosphatase	91%	68%	53%	95%	74%
Alkaline phosphatase ($>2 \times \text{N}$)	73%	86%	67%	89%	82%
Aspartate transaminase	64%	82%	58%	85%	77%
Alanine transaminase	55%	82%	55%	82%	74%
Common bile duct stenosis*	87.5%	50%	44%	90%	62%

*Only on 26 patients with successful cholangiogram.

the definition was restricted to radiological narrowing of the common duct to less than a certain diameter, or to narrowing which results in dilatation of the proximal biliary tree. Only when such a definition is agreed can we hope to rationalise our understanding of the extent of the problem and its treatment. Persistent abnormality of the liver function tests should alert the clinician to the possibility of common bile duct stenosis and biliary radiology should be mandatory. Jaundice in an alcoholic may be diagnosed as alcoholic hepatitis or cirrhosis when unsuspected extrahepatic biliary obstruction is the cause⁵ and conversely hepatocellular disease may mimic the biochemical features of extrahepatic biliary obstruction.²¹ Despite alcohol being the putative aetiological factor in 77% of our patients the incidence of significant alcoholic liver disease (5%) was small and an infrequent cause of biochemical derangement compared with Bradley and Salam's experience.¹⁷

The results of our study show that, even in the presence of radiological stenosis of the common bile duct, liver enzyme abnormalities do not always reflect extrahepatic biliary obstruction, the presence of which may only be confirmed by liver biopsy. All but one of the 11 patients with histological features of extrahepatic biliary obstruction had abnormal liver function tests. Therefore, even in the presence of radiological common bile duct stenosis, normal liver function tests suggest that at that particular time extrahepatic biliary obstruction is unlikely and that liver biopsy and biliary bypass surgery are not indicated. This situation can, of course, change and these patients should be kept under review and have their liver function tests monitored regularly.

The accepted indications for drainage of the biliary tree in chronic pancreatitis are the relief of biliary tract symptoms such as obstructive jaundice or cholangitis.^{5, 22, 23} Jaundice was the indication for surgery in six of our patients but two did not undergo a formal biliary bypass and we would now regard this decision as incorrect in the light of their post-operative course. Transduodenal sphincteroplasty is inadequate as a biliary drainage procedure in chronic pancreatitis because the stenosis length exceeds the length of sphincteroplasty that can safely be undertaken.^{5, 23} Pseudocysts alone rarely produce biliary obstruction in chronic pancreatitis and a fibrotic stenosis usually coexists;^{17, 23-25} in retrospect a formal biliary enteric bypass should have been done in our patient at the time of cystogastrostomy to ensure adequate drainage of the common bile duct.

The role of surgery in anicteric patients with common bile duct stenosis who manifest persistent alkaline phosphatase rise is more controversial. Sarles and Sahel⁷ consider that these patients,

because they have a more dilated proximal bile duct, may have more prolonged bile duct obstruction than those who present with jaundice. Biliary enteric bypass may be considered in such patients to prevent secondary biliary cirrhosis which, although a rare complication in most series, was reported in 10% of one series of 50 patients undergoing peroperative liver biopsy.²⁶ In another series an incidence of 29% was recorded in 24 patients with common bile duct stenosis complicating chronic alcoholic pancreatitis, these patients having been detected by screening a larger group for persistent alkaline phosphatase rises.⁶ It is probable that biliary cirrhosis usually develops over many years in neglected or unsuspected biliary obstruction but rapid progression from cholestasis to biliary cirrhosis over the space of a year has been documented.^{5, 23} Secondary biliary cirrhosis was not seen in any of our patients. Portal tract fibrosis, a finding which others have observed commonly,^{6, 22} was present in four of our cases. In three of these there were fibro-obliterative lesions of the interlobular bile ducts indicating the development of a secondary sclerosing cholangitis. In these three cases we would envisage a greater likelihood of progressive cholestatic liver disease, which in the absence of fully adequate biliary drainage, would result in secondary biliary cirrhosis.

Three of our patients had a biliary enteric bypass carried out for serum alkaline phosphatase rises in association with common bile duct stenosis but only one had features of extrahepatic biliary obstruction on biopsy. Isolated rises in alkaline phosphatase was, therefore, a less common indication for biliary enteric bypass than jaundice and less specific for the presence of extrahepatic biliary obstruction.

Of the six patients undergoing biliary enteric bypass, two of the three treated by cholecystjejunostomy had recurrent jaundice. While cholecystjejunostomy may be adequately palliative in obstruction caused by pancreatic carcinoma it is inappropriate in chronic pancreatitis. Others have reported similar problems^{27, 28} and its use should be abandoned. Neither would we recommend the approach of prolonged bile duct drainage by T-tube, in combination with a pancreatic duct or cyst drainage procedure, as suggested by Newton *et al.*²⁵ Endoscopic stenting of the stenosis is likely to have a role in ill patients unfit for surgery. Choledochoduodenostomy has been recommended most often as the bypass procedure of choice, not least because it is the easiest form of bypass to do and is the most 'physiological' procedure.¹⁷ Recurrent cholangitis may be a problem in some 5% of cases²⁹ and we now prefer Roux-en-Y choledochojejunostomy or hepaticojejunostomy for longterm biliary drainage.

Persistent abnormality of the liver function tests in

patients with chronic pancreatitis should prompt ultrasound scan and full radiological assessment of the biliary tree. Persistent jaundice in the presence of radiological common bile duct stenosis is a strong indication for biliary enteric bypass but pre-operative liver biopsy is suggested in those with isolated rises in alkaline phosphatase. There is no place for routine biliary enteric bypass during surgery for chronic pancreatitis.

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