Cystic disease of the liver and biliary tract

A Forbes, I M Murray-Lyon

Abstract
The widespread availability of ultrasound imaging has led to more frequent recognition of cystic disease affecting the liver and biliary tract. There is a wide range of possible causes. Cystic disease of infective origin is usually caused by an Echinococcal species, or as the sequel of a treated amoebic or pyogenic abscess. The clinical and radiological features are often then distinctive and will not be dwelt upon in this review, except in respect of their contribution to the differential diagnosis of non-infective disorders. The principal non-infective cysts can be conveniently divided between the simple cyst, the polycystic syndromes (usually with coexistent renal disease), Caroli’s syndrome, and choledochal cysts. The overlap between constituent members of these groups, and the association of cystic disease with hepatic fibrosis (especially with congenital hepatic fibrosis) has attracted considerable attention, and it has been suggested that they may all be considered to belong to a hepatobiliary fibrocystic continuum. In addition there are a variety of cystic neoplasms and a miscellany of unusual forms.

Investigation and diagnosis
Large cystic lesions may be recognised clinically, but in most cases will be found at ultrasound examination undertaken because of symptoms, or laboratory screening tests suggestive of hepatobiliary disease; cysts are not infrequently an incidental finding when scans are done for unrelated clinical problems.

An accurate differential diagnosis will often be possible from ultrasonography alone. Most commonly, one or more clearly defined echo-lucent spaces are identified within the liver substance. When these have thin walls and reduce the signal from more distant structures, the most likely diagnosis is of simple cyst and further investigation is usually unnecessary. It is suggested, however, that magnetic resonance (MR) imaging may be particularly helpful in doubtfull cases. Thicker walled single or multiple cysts with a multilayer or laminated margin are likely to be hydatid, and the presence of daughter cysts within the lesion is virtually pathognomonic. A supportive history and positive serology will usually allow confirmation of this diagnosis. Aspiration of presumptive hydatid cysts is contra-indicated because of the perceived high risk of anaphylaxis if cyst contents spill into the peritoneum, and there is usually no need to consider aspiration if hydatid disease is suspected. The hazard has perhaps been over-emphasised, however, and if hydatid disease is unlikely and cysts have inconclusive sonographic appearances, aspiration for microbiological and cytological examination is warranted. Several reports—(for example, and our own unpublished observations)—of needle diagnosis of unsuspected hydatid disease, and even therapy by ultrasound guided transcutaneous injection of sclerosant, indicate that if the transhepatic route is taken the risk of morbidity is low.

Distinction of abscess from cyst is relatively simple if an abscess has viscous echo dense contents with a thick wall and densely compressed surrounding hepatic parenchyma. Percutaneous aspiration allows confirmation of the diagnosis, provides material for microbiological examination, and may be of major therapeutic benefit. Positive blood cultures or amoebic serology may, however, render aspiration superfluous, given that small single abscesses can be effectively managed with systemic antimicrobials alone. Open surgical drainage remains necessary for optimal results in some patients with chronic multiloculated abscesses.

Cystic lesions in continuity with the biliary tree or with vascular structures may be identified by ultrasound (the latter particularly so with Doppler probes), but it will usually be necessary to obtain contrast studies (by ERCP or angiography) for complete diagnosis. In this context computed tomography and MR images of the hepatobiliary region do not appear at present to offer many advantages over high resolution sonographic examination. The interested reader is referred to one of a number of illustrated reviews in the radiological literature.

Liver biopsy tends to be avoided in the investigation of cystic disorders, a stance certainly justified when there is suspicion of hydatid disease, and probably so when imaging suggests choledochal cyst, but the recognition of underlying fibrosis is then less likely, and the clinician is denied potentially important prognostic information.

SIMPLE HEPATIC CYSTS
Benign non-parasitic cysts of the liver, once considered rare because they are generally small and asymptomatic, are more commonly shown by modern imaging (prevalence between 0·1% and 2·5%); more so in women (female: male ratio 1·5:1), more often in the right lobe, and probably of congenital origin. The cysts are lined by biliary columnar epithelium, but it is relatively unusual for the fluid contents to be bile. If the typical appearances at sonography described above are seen, no further investigation or treatment is required. The sensitivity of aspiration cytology in potentially neoplastic cysts with no definite solid component is low, but may be improved by assay of cyst contents for tumour markers such as
Cystic disease of the liver and biliary tract

POLYCYSTIC DISEASES

Adult polycystic disease, of autosomal dominant inheritance with high penetrance, may present at any age with renal manifestations, but although hepatic involvement is common, clinically significant liver disease is rare (<15%), and does not usually affect the natural history.24 Hepatic cysts are not often seen before puberty but become more frequent with increasing age (<20% in those under 30, 25, 26, >75% in those over 7025, 30); they are more common in women,24 especially those with children. When liver disease occurs it usually accompanies relatively advanced renal disease (mean creatinine clearance two thirds of those without hepatic cysts.31) Polycystic liver disease may, however, occur in the absence of significant renal involvement. The cysts are lined by biliary type epithelium which retains a functional response to secretin.32 Their pathogenesis (akin to that of simple cysts) is considered to reflect failed involution of excess intralobular bile ducts during embryological development.33, 34 Liver biopsy shows portal tract fibrosis and numerous cystic passages caused by dilated channels; the hepatic parenchyma is otherwise normal but it is not unusual to find Von Meyenburg complexes in non-cystic parts of the liver (see below). Overt congenital hepatic fibrosis (see below) certainly occurs25 but is unusual.

Apparently spontaneous infection of hepatic cysts is described, usually with gut derived organisms, and prompt recognition and drainage greatly reduces the mortality which may exceed 75% with antibiotic therapy alone.35 Mechanical cholestasis caused by the cysts is rare,36 but a common topic of case reports: it remains unclear why the pressure within the cysts should rise to cause obstruction, but hormonal responsiveness37 may be of relevance. Relief of biliary obstruction may be satisfactorily provided by percutaneous aspiration.38 In advanced disease portal hypertension responsible for ascites and variceal haemorrhage can become problematic39: good results may be obtained from portosystemic anastomosis. In the majority of cases, however, management will be that of chronic renal failure with consideration of renal transplantation. If there are problems related to the sheer size of the liver or coexistent symptomatic portal hypertension, then many units will now take the opportunity to carry out double organ grafts from the same donor: good results are reported, but disappointingly King's was not the first unit to publish specifically on this topic.35

The autosomal recessive form of polycystic disease usually presents in infancy with renal failure and massive kidneys: these patients rarely have significant liver disease. Presentations later in life are associated with less aggressive renal disease, but with a progressively higher frequency of congenital hepatic fibrosis and likelihood of portal hypertension.40 Patients with the mildest renal involvement are perhaps most likely to have an hepatic presentation. The clinical diagnosis based on renal enlargement and hepatomegaly is supported by biochemical evidence of renal failure, relatively normal liver function, and the demonstration of renal cysts on ultrasound scanning: the hepatic cysts are often too small to be identified sonographically. Histologically, the hepatic cysts appear identical to those of autosomal dominant cases. Liver Unit authors were responsible for the recognition of a number of other renal cystic disorders associated with hepatic fibrosis,41 the latter apparently indistinguishable from congenital hepatic fibrosis.

CONGENITAL HEPATIC FIBROSIS

Congenital hepatic fibrosis deserves its present inclusion because of the frequency with which it is associated with cystic disease. In its overt form it usually presents in childhood with complica-
tions of non-cirrhotic portal hypertension (especially bleeding), but may present in adulthood; asymptomatic forms are encountered at all ages. It is most often associated with the recessive form of polycystic kidney disease, but at least two groups give convincing accounts of an association between congenital hepatic fibrosis and autosomal dominant polycystic disease. Equally, in a few cases the kidneys are apparently normal. Histologically there is a considerable increase in fibrous stroma distributed in broad bands throughout the liver with focal epithelial components and islands of normal lobular architecture. Such 'pure' congenital hepatic fibrosis may be disguised by coexistent histological features of polycystic disease, and often by the presence of Von Meyenburg complexes. These biliary microhamartomata lie within dense fibrous stroma and surround epithelially lined irregular spaces which may contain bile. The complexes expand within or adjacent to the portal tracts and, as they are usually multiple, may be confused with micro-metastases. They may be responsible for portal hypertension without more generalised fibrosis.

The Liver Unit described the association of congenital hepatic fibrosis with intra and even extra hepatic biliary dilatation producing a picture identical to Caroli’s syndrome except that in that situation there is no fibrosis of the congenital hepatic fibrosis pattern.

A recent autopsy study supported the association of fibrosis with cystic disease added the new observation that benign hepatic adenomas are associated with non-parasitic cysts; that the description is of polycystic disease rather than of simple cysts seems likely, but the significance of the association is probably of greater importance than the semantics of diagnosis.

**CAROLI’S SYNDROME**

Congenital dilatation of the intrahepatic bile ducts without obstruction was recognised by Caroli in 1958. Pure Caroli’s syndrome remains an unusual diagnosis, with fewer than 150 cases in the world literature. A hereditary component – possibly recessive autosomal transmission – is supported by a report of the condition in two sisters. The saccular cystic dilations more commonly affect the left lobe, and may be associated with biliary stasis, cholangitis, stone formation (in about 25%), and pain. Involvement of the extra hepatic bile ducts is unusual. Although symptoms may begin in childhood and progress remorselessly via fibrocholangi-10matisis to cirrhosis, a significant proportion of affected individuals will remain asymptomatic. The diagnosis should be seriously considered in any child with cholangitis. The combination of ultrasonography and ERCP lead to the diagnosis, although there is a small risk that the latter may reprecipitate cholangitis. Management depends on correct diagnosis and on the extent of liver involvement. Symptomatic disease affecting only one lobe of the liver can usually be successfully resected, albeit with considerable difficulty if extensive intrahepatic cholelithiasis has to be dealt with concurrently. More extensive resection, with hepatojejunal anastomosis, is also possible for multilobular disease, and the option of orthotopic transplantation remains for the end-stage patient with bilobar disease and/or cirrhosis, so long as sepsis can be controlled preoperatively.

Caroli’s syndrome may be complicated by pancreatitis, obstructive portal lymphadenopathy or extra biliary sepsis, and advanced disease is usually associated with fibrocholangi-10matisis; itself often responsible for portal hypertension.

Primary sclerosing cholangitis has a number of common features with Caroli’s syndrome, especially when dilated duct segments take on a cystic appearance. Although a firm diagnosis is usually possible there are occasions when the two conditions cannot be clearly distinguished, and it is possible that an overlap syndrome exists.

Caroli’s syndrome is certainly associated with hepatic fibrosis, and a report of Caroli’s syndrome in renal polycystic disease suggests again that the distinctions between the different cystic diagnoses are not fundamental but more a matter of degree. Also consistent with this notion, is the important observation that Caroli’s syndrome is probably a premalignant condition; frank malignancy may be preceded by biliary epithelial dysplasia.

**CHOLEDOCHAL CYSTS**

Choledochal cysts account for approximately 1% of all benign biliary disease and as recently as 1980 less than 40% were diagnosed preoperatively. They are primarily of concern to paediatricians and paediatric surgeons as more than 60% present before 10 years of age. The frequency is highest in Japan but appears relatively uniform across the rest of the globe. Numerous large historical series have been reported, but this relatively common rarity has continued to exert an appeal to authors and editors alike, because several hundred papers can be identified from Index medicus over the past five years alone – many of these being single case reports. A consensus on management is nevertheless emerging despite the absence of controlled trials. Almost all authorities now use modifications of the Alonso-Lej classification, typically dividing choledochal cysts into four groups (Fig 1). The commonest (type I) comprises a fusiform or saccular dilatation of the extrahepatic biliary tree with a normal or stenotic distal common bile duct. Less often cysts appear as common bile
Cystic disease of the liver and biliary tract

Many patients will initially respond to simple medical measures, allowing time for careful assessment. Continued conservative therapy, provision of internal (or very occasionally external) drainage, or excision of the cyst must then be considered. The anatomy will usually be readily apparent from ultrasound scanning and ERCP, but will in a few cases remain enigmatic despite the full range of currently available radiological techniques. Treatment options should be considered in the light of the collected historical series. It appears that about 50% of patients having drainage procedures will need reoperation—usually because of recurrent sepsis or cholestasis, and one author makes the startling claim that his study 'provides conclusive evidence that any anastomosis of cyst wall to the gastrointestinal tract will ultimately result in stricture and cholangitis'. Moreover, at least one group has found (admittedly without taking full account of the technical considerations that determined the original operation), that the perioperative mortality is substantially higher for drainage procedures than for excision (8-6% v 0%). Excisions may vary between a cholecystectomy like removal of a type II cyst to a virtual extirpation of the biliary tree; most authors now prefer hepatojejunostomy. Excisions are not without their complications, however. One of the most experienced groups recently described a reoperation rate of nearly 10% in 73 excisions—although all seven ultimately did well. Major revisions were needed in most cases—usually conversion from hepatoduodenostomy to hepato-Kouy-Y-jejunostomy after early haemorrhage/leak or late stenosis of the original anastomosis.

Carcinoma (adenocarcinoma in more than 90%) is now well recognised as a complication of choledochal cysts. The life time risk for the individual may be as high as 50% if non- resectional surgery has been carried out. Bile stagnation, continual pancreatic reflux, and related chronic ulceration and regeneration of the cyst epithelium are thought causally relevant. Investigation of an 18 year old patient with a choledochal cyst showed an increase in secondary bile salts (most of which were unconjugated) within the cyst fluid, despite an entirely normal bile salt pattern in intrahepatic bile. The authors attribute this to bacterial colonisation within the cyst, and speculate that this caused the patient’s biliary epithelial metaplasia and could contribute to the development of neoplasia. It is probable that the cancer risk is substantially higher in patients presenting for the first time as adults, and attributed risks of between 5 and 40% have been suggested. Review of the computed tomography files in one Japanese institution revealed that eight of 35 consecutive adult cases of choledochal cyst had complicating malignancy. It must be noted that the studies with the longest follow up periods have consistently given the highest figures. Although the most common site of origin for malignant change is the posterior cyst wall, it is evident that there is a biliary ‘field’ defect as primary carcinoma may occur in biliary tissue uninvolved in the cyst, a striking 46% occurring in apparently normal gall bladder in one series.

duct diverticula (type II), are contained within the intraduodenal course of the duct (type III), or are more generalised, involving both intra and extrahepatic duct systems (type IV) (Fig 1). There is evidently a point at which it becomes difficult to distinguish between intrahepatic choledochal cyst and Caroli’s syndrome; reports claiming heterogeneity of Caroli’s syndrome apparently fail to appreciate the semantic nature of diagnosis in this situation. It is probably reasonable to consider choledochal cyst a part of the continuum already discussed in respect of the purely intrahepatic cystic conditions.

It is almost certain that choledochal cysts are of congenital origin, but the pathogenesis is less clear. It has been speculated that there is a differential abnormality in biliary epithelial proliferation in the embryo such that the solid core of proto-bile duct takes on a cystic form; there is, however, no good evidence to support this. It is probable that reflux of pancreatic juice into the biliary tree is of relevance, however. A very large proportion of (and possibly all) patients with choledochal cyst have an unusually long common channel between the junction of the common bile duct and the main pancreatic duct and their joint outflow into the duodenum (Fig 2). The increased intraduodenal pressure associated with this anomaly predisposes to reflex and may also be associated with ectasia of the common channel (or indeed with pancreatitis). High concentrations of pancreatic enzymes within cyst fluid are common and pancreatitis may be diagnosed erroneously when hyperamylasaemia also occurs. A recent report of choledochal cyst in mother and daughter, both of whom had a long common channel and the same type of cyst suggests that a hereditary element is important in some cases. Concurrent hepatic fibrosis has not attracted much attention, but certainly occurs, and lends support to the inclusion of choledochal cystic disease in the fibrocytic continuum.

Choledochal cysts may remain asymptomatic for many years (and possibly for life) but the majority will at some time cause one or more of the classical triad of pain, obstruction and palpable mass, often in association with cholangitis, or exhibit one of the less common features enumerated by the Department of Surgery at King’s, such as ascites, variceal haemorrhage, or biliary peritonitis from spontaneous rupture.
Prognosis once carcinoma has occurred is uniformly poor.

It is reasonable to conclude that choledochal cysts should always be excised with as complete resection of the (extrahepatic) biliary tree as possible. Such a policy should minimise postoperative cholangitis/cholestasis and achieve a low frequency of reoperation; it should also, with luck, eliminate the risk of malignant transformation within retained cystic components, or apparently normal more proximal biliary epithelium. When comprehensive excision implies a major pancreatic resection as well as dissection up into the liver, however, dogmatic views may have to be tempered, and especially so if the patient is asymptomatic!

**CYSTIC NEOPLASIA**

Hepatic cysts are not often neoplastic, but cystic tumours are recognised occasionally. Multilocular cystadenoma occurs almost exclusively in middle aged women who typically present with a rapidly growing upper abdominal mass; about one third develop clinical cholestasis. The distinction from simple cysts is straightforward histologically but less obvious clinically or radiologically: the presence of multiple cystic areas (usually several small lesions around a larger cyst), the presence of biliary obstruction, and the rate of progression are useful pointers. Surgical resection is advised as malignant transformation may occur.

Myxomatous tumours of the liver are evidently very rare, but may be responsible for a painful mass: the single reported case was probably benign. Benign cystic hepatoblastoma occurs in preschool children, usually presenting as an abdominal mass with multilocular cysts on investigation; transformation to cystadenocarcinoma may occur if unresected. Malignant cystic hepatoblastoma is a distinct and very rare paediatric tumour where the malignant component of the tumour is stromal rather than epithelial, the prognosis is poor.

Cystic metastases from carcinoma of the ovary and kidney, and from intra-abdominal sarcomas are also described. The malignant nature of these lesions is usually apparent from associated parenchymal disease, or from the classical sonographic appearance of a malignant cyst, with thick irregular walls studded by nodules. The diagnosis will usually be clarified by aspiration cytology, but serial scanning is almost as helpful as cystic metastases typically enlarge rapidly.

**OTHER CYSTIC DISORDERS**

Various other cystic disorders have been described, of which 'ectopic' pancreatic pseudocyst is perhaps the most common, but accurate diagnosis is otherwise unusual without histological examination of material obtained at surgery or autopsy. Any list is unlikely to be comprehensive.

Occlusion of small portal vein branches from any cause (particularly compression by adjacent hepatic tumour) can produce areas of apparent infarction manifest as small cystic areas; as tissue necrosis is absent these are now generally known as pseudoinfarcts of Zahn and have no prognostic significance in their own right.

Peliosis hepatis was originally described in the terminal cachexia of disseminated tuberculosis, but is now most often seen in women on combined contraceptive pill. Work from this unit clarified a link between peliosis and long term androgen therapy, and associations with other conditions such as HIV infection are also recognised. It is probably underdiagnosed as investigation is embarked upon only in those who develop hepatomegaly or abnormalities of liver function. Histologically there are blood filled cavernous cysts in continuity with the sinusoids. Cysts vary in size but may reach 5 mm in diameter and allow sonographic recognition. Peliosis is usually harmless, and it will often regress if a predisposing factor can be withdrawn. Rarely, liver failure or hepatic rupture may occur. Sinusoidal ectasia appears to be a milder form of peliosis and may represent its earliest manifestations.

Less than 20 cases of ciliated hepatic foregut cyst have been described. They are thought analogous to bronchogenic cysts, with which they share a 'columnar' mucous-secreting lining of stratified columnocuboidal lining with a muscular wall and surrounding fibrous tissue. Characteristically they have a subcapsular site and are usually less than 3 cm in diameter. The sonographic findings include heterogeneous echogenic semi fluid contents (which may at first sight appear solid) within a well demarcated lesion, and aspiration reveals viscous mucinous exudative fluid. They are non-neoplastic and require no treatment if the diagnosis is certain.

Endometriosis may also be responsible for hepatic cysts, successfully treated in the first report by resection. Had the diagnosis been realised preoperatively might hormonal therapy have sufficed?

Post traumatic hepatic cysts are recognised in addition to the cystic spaces that may remain after successful non-drainage treatment for liver abscess. A similar phenomenon has been reported from the Liver Unit after apparently curative hepatic artery embolisation (for metastatic apudoma), and is probably not uncommon after this intervention.

Cystic fibrosis is not, it appears, associated with higher frequencies of hepatobiliary cysts than would be expected by chance.

**Conclusion**

There is much in the collected literature on hepatic and biliary cystic disorders to suggest common threads in aetiology, pathogenesis, clinical presentation, complications and management (assuming that cysts of infective or neoplastic origin are excluded). The strong association of adult polycystic kidney disease with polycystic liver disease is not complete, and it need not be assumed that the hepatic cysts are encoded for by the same gene defect. The various overlap syndromes earlier alluded to allow the possibility that even if polycystic liver disease is also of autosomal dominant inheritance, it has variable expression with relatively low penetrance. Almost all hepatobiliary cysts are lined
by biliary epithelium or epithelium with strong biliary characteristics. All most probably develop in the prenatal period (and clinical presentation is generally common in childhood). All are more common in women and there are suggestions that hormonal factors may be relevant. All share an association with hepatic fibrosis, although the strength of the association admittedly varies according to the major characteristics of the cystic disorder. Most, and probably all, of the cysts render a substantially increased risk of biliary tract malignancy (and perhaps hepatic neoplasia also), the added risk appearing to be greatest where the cyst is in communication with the biliary tree. It is unusual for cysts themselves to be responsible for symptoms, but the complications, including those of portal hypertension, that lead to presentation are common to all varieties. Management can usually afford to be expectant except for chole-do-}
Forbes, Murray-Lyon


