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Biliary cystic disease: the risk of cancer

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Abstract
Congenital choledochal cysts carry a risk of cancer, probably as a result of a sequence of pancreatobiliary reflux, inflammation, dysplasia with or without intestinal metaplasia, and invasive carcinoma. A combination of biliary stasis due to poor drainage of a stagnant pool of bile and increased mutagenicity of the bile acids may be ultimately responsible. There is very frequently an anomalous pancreato-biliary ductal junction, and the reflux of pancreatic juice into the bile duct is thought to play a central role in the process of carcinogenesis. The risk of cancer is low in childhood (under 1% in the first decade), but shows a clear increase with age (over 10% in the third decade). The implication for management is that total excision of the extrahepatic biliary tree at risk remains the gold standard for management of these cysts, and simple bypass in infancy or childhood leaves the risk of cancer, though possibly diminished, still significant.

Key words Choledochal cyst · Cancer · Congenital anomalies · Bile ducts

Introduction

The incidence of choledochal cysts in the West is between one in 100000 and one in 190000 live births. In Japan, it accounts for one in 1000 admissions to hospital, compared with one in 13000 in the United States. There is a 3 or 4:1 female preponderance.[1]

Etiology

These are true congenital lesions, and some are now diagnosed by antenatal ultrasound. A frequent finding is an anomalous junction between the pancreatic duct and the bile duct (APBDJ), with a common channel from a few millimeters to several centimeters in length. This anomaly was seen in all 39 cases examined by Komi et al.,[2] and has been classified into several subtypes by this group.[3] However, its absence does not preclude the diagnosis of choledochal cyst. The APBDJ results in free reflux of pancreatic juice into the bile duct. Experimental reproduction of this lesion leads to common bile duct dilatation with weakening of the duct wall and inflammatory changes in the endothelium,[4] and this may also be a key factor in the pathogenesis of malignant change in the cysts.

Classification

The classification by A1onso-Lej et al.[5] is generally used. The commonest is type 1, which has been subdivided into a cystic or a fusiform dilatation of the common bile duct. Large cysts are easy to identify (Fig. 1), but subtle forms of fusiform dilatation are being recognized increasingly, in association with low-grade obstruction or recurrent pancreatitis. The clue may lie in the anomalous junction of the pancreatic duct and the bile duct (Fig. 2). Type 2 is a simple diverticulum and type 3 a choledochocele in the distal duct. Type 4 is the second most common, with both extra- and intrahepatic cysts. Type 5 is confined to the intrahepatic ducts, and may merge into the syndrome of Caroli's disease, which, in turn, is associated with congenital hepatic fibrosis.

Pathology

The ductal epithelium in choledochal cysts is seldom completely normal. The duct may undergo progressive chronic inflammation, with ulceration and areas of loss of biliary epithelium, associated with previous attacks of cholangitis. The wall may become thickened and

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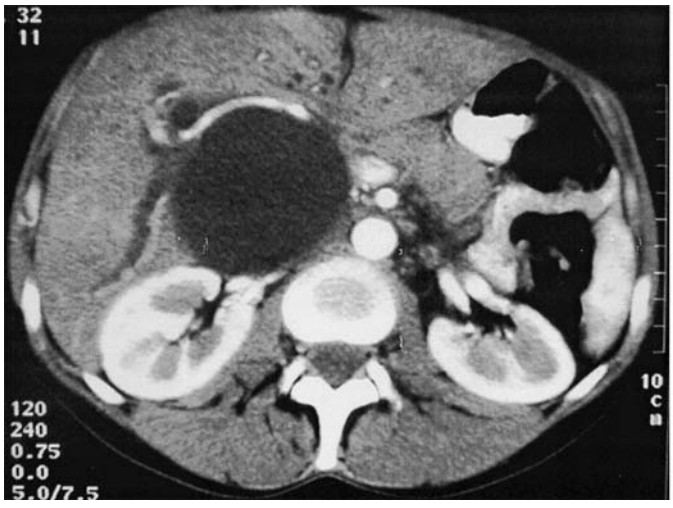

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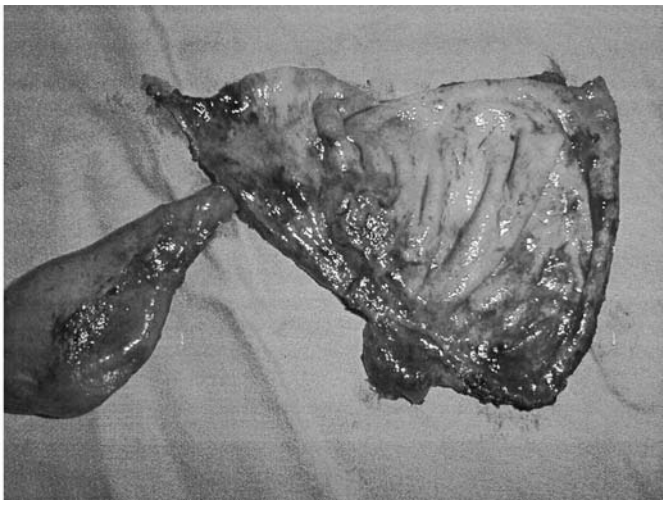

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Fig. 1. a Computed tomography (CT) scan showing a large choledochal cyst. There is dilatation of the intrahepatic ducts due to obstruction distally within the cyst. **b** Excised choledochal cyst from the patient whose CT scan is shown in **a**. The gallbladder can be seen attached towards the upper end of the excised cyst, which has been opened. There are areas of inflamed mucosa, but no malignancy or dysplasia was identified

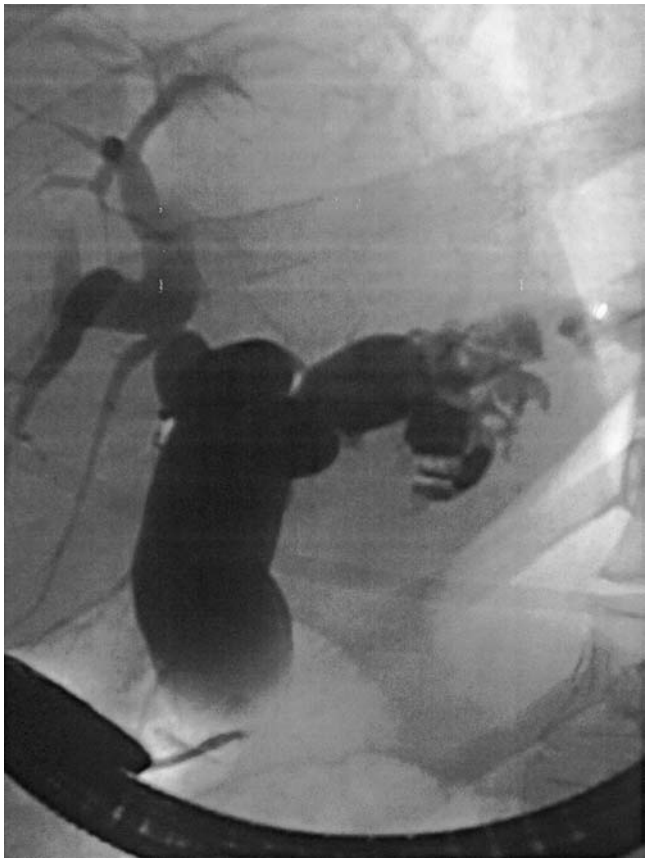

Fig. 2. Endoscopic retrograde cholangiopancreatogram (ERCP) showing fusiform dilatation of the extrahepatic bile ducts, with intrahepatic dilatation also. The distal pancreatic duct can be seen, and there is the suggestion of an anomalous junction between the pancreatic duct and the bile duct (APBDJ), though not fully delineated on this film

fibrosed. Most cysts contain high levels of biliary amylase and/or lipase, though this is not an absolutely invariable finding. Epithelial hyperplasia is a frequent finding, accompanied by round-cell infiltration. In one series, increased thickness of the wall with fibrosis was observed histologically in the resected bile ducts of all of 40 patients with choledochal cysts.[6] These workers recognized two categories of change: 22 of 26 patients (84.6%) who had bouts of abdominal pain had mainly epithelial hyperplasia with round-cell infiltration (glandular type), while 11 of 15 patients (73.3%) with persistent jaundice showed, predominantly thickening of the wall with fibrosis (fibrotic type). Amylase activities in the common bile duct bile of glandular-type cases were significantly greater than those of fibrotic-type cases.

Presentation

The classical presentation in infancy is a triad of jaundice, pain, and a mass in the right hypochondrium. In adulthood, cholangitis with or without obstructive jaundice is more common, and both children and adults may present with recurrent pancreatitis. It is important to be aware of the possibility of a subtle fusiform dilatation of the bile duct in patients with otherwise unexplained recurrent acute pancreatitis, and to seek evidence of an APBDJ. Perforation has been reported, and a number of patients have presented with jaundice in pregnancy, presumably due to distortion or compression of the cyst causing distal obstruction. There is no specific diagnostic syndrome for malignancy in cysts, and the presentation may be insidious or totally silent.

Investigations

There are no specific laboratory tests, and the initial diagnosis is usually made by ultrasound. Focal thickening of the cyst wall should raise the suspicion of cancer. Biliary imaging is essential, and the diagnosis is frequently confirmed by endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC). Either will allow definition of the cyst, but ERCP is more likely to demonstrate the APBDJ. ERCP must be undertaken with caution to avoid infection of the cyst or precipitation of pancreatitis. Magnetic resonance cholangiopancreatography (MRCP) has begun to supersede ERCP in many centers, and has the benefit of being entirely noninvasive.

Management

The old treatment of cyst-duodenostomy relieves jaundice but does not eradicate biliary stasis nor remove the risk of malignancy. Endoscopic sphincterotomy may also fail to reduce the rate of complications. The type 3 cyst (choledochocele) may be so treated, or is occasionally removed by a transduodenal approach. For all other extrahepatic cysts, the ideal treatment is excision of the entire dilated extrahepatic biliary tree from the confluence down to the biliary-pancreatic ductal junction, taking care to avoid pancreatic damage. Removal of as much of the cyst as possible is important, to minimize the continuing risk of malignant transformation[7] (see below). It is generally possible to lift the whole extrahepatic biliary tree off the portal vein safely, and reconstruct the hepatic duct by an hepatico-jejunostomy Roux-en-Y. When the upper limit of the cyst involves the hepatic duct confluence, it is reasonable to compromise and leave a small cuff of the confluence intact to allow a safe and durable anastomosis.

Malignant change

It has been noted above that the epithelium of the cysts frequently shows evidence of previous inflammation, and this may lead to areas of dysplasia which may be the precursor of invasive malignancy. The mechanism is unclear, and its relationship to pancreatic reflux has not been fully defined. Biliary stasis predisposes to formation of secondary bile acids, which are mutagenic. The risk increases with duration of exposure: malignancy is hardly ever seen in cysts removed in infancy, and the mean age of presentation is 32 years.

Carcinoma in association with bile duct cysts was first reported in 1944.[8] Tumors may develop anywhere within the biliary tree, but more than one-half occur within the cyst itself.[9] Tumors are most common in type 1 and type 4 cysts,[1] i.e., those with fusiform dilatation of the intrahepatic and/or extrahepatic ducts, but they also occur in type 5 (Caroli's disease).[10]

The commonest tumor type is adenocarcinoma (cholangiocarcinoma), though other types have been reported, including squamous cell carcinoma.[1] It must be noted that cancer in other types of intrahepatic cysts (simple cysts or polycystic disease) is exceedingly rare, and should not direct decisions regarding therapy.[11]

The younger the patient at presentation of the choledochal cyst, the lower the incidence of subsequent malignant change: the risk is less than 1% if the choledochal cyst presents within the first decade of life, but increases to 14% if presentation is delayed beyond 20 years of age.[12] The youngest reported patient with adenocarcinoma in a choledochal cyst was 17 years old, and she had undergone biliary bypass 8 years earlier.[13]

Preoperative diagnosis of carcinoma is very rare and the prognosis is poor, less than 10% being resectable.[9] Ishibashi et al.[7] reported biliary carcinoma in 9 of 48 patients presenting with choledochal cysts. Six of these died from recurrence with a mean survival time of 13 months, while 3 patients were alive and free from recurrence 2 months, 1 year, and 7 years after operation.

While early drainage may have beneficial results by reducing biliary stasis and cholangitis and reducing contact with possible carcinogens, it would be logical to expect resection to reduce the incidence further, not only by removing the most vulnerable part of the mucosa but also by providing better biliary drainage and preventing reflux of pancreatic juice. In Ishibashi's series of 48 patients managed over a 21-year period,[7] 39 had no carcinoma at first admission, and 37 of these underwent complete or near-complete cyst excision with hepatico-jejunostomy. In these 37 patients, no carcinoma developed in the remnant proximal hepatic duct or the terminal bile duct after a mean follow-up of 9.1 years.

We reported a series of seven patients with complications of choledochal cysts in adulthood:[14] one had malignant change, and was typical in presentation, age, sex, extent of tumor, and outcome. She was a 32-year-old woman who presented with severe epigastric and back pain, followed by obstructive jaundice. A large epigastric mass was palpable, and ERCP revealed a choledochal cyst 15 cm in diameter, with an irregular pancreatic duct. At laparotomy to excise the cyst, a 6-cm ulcerating tumor was found obstructing the distal lumen. Frozen section showed an undifferentiated adenocarcinoma, and this was subsequently confirmed on paraffin section. There was also extensive lymphadenopathy. The cyst was excised and the ducts reconstructed by hepatico-jejunostomy Roux-en-Y. Despite postoperative chemotherapy, she died of diffuse carcinomatosis some weeks later.

Pathogenesis of malignant change

Experimental studies in dogs have simulated an APBDJ by means of a pancreatico-cholecystostomy.[15] After 24 to 41 days, cylindrical common bile duct (CBD) dilatation, up to 3.28 ± 2.48 times diameter, was found in 23/29 (79%) of the dogs, with biliary stones in 3/29 (10%). The amylase level and levels of phospholipase A2 in the bile were elevated in all 25 dogs tested. Inflammatory changes were observed in all specimens, with intramural glandular structures in 17/25 (68%) of gallbladder specimens and 10/25 (40%) of CBD specimens. DNA ploidy abnormalities were found by cytofluorometry in both gallbladder and bile duct epithelium. Similar ploidy abnormalities were found by the same workers in two clinical cases of choledochal cyst without malignant change.[16] Dot-blot hybridization and immunohistochemical study did not reveal any mutations in the c-Ki-ras gene, or any overexpression of the p53 protein in the specimens.

Using a similar model, gallbladder bile acids were studied 14 months after pancreatico-cholecystostomy, with or without pancreatic duct ligation as control. The fraction of cholic acid tended to be lower, and that of deoxycholic acid slightly higher in APBDJ-dogs, while the percentage of ursodeoxycholic acid in APBDJ-dogs was significantly decreased compared with that in the control and normal dogs. A high frequency of DNA strand breaks was shown in only two out of seven APBDJ-dogs, and in these two dogs, the cholic acid percentage decreased and that of deoxycholic acid greatly increased. These findings suggest that the alteration of bile composition in APBDJ may cause frequent DNA strand breaks and repair which might lead to gene mutation and biliary tract carcinoma. Further studies suggested that pancreatic juice enzymes and bacteria infecting the biliary duct can deconjugate detoxified mutagens in the bile and induce mutagenicity of the bile in APBDJ dogs or patients.[17]

The same group carried out immunohistochemical studies on excised specimens of choledochal cysts.[2] An APBDJ was observed in all 39 cases examined. Among the total of 47 patients, 5 (10.6%) had biliary carcinoma. Among 24 adults, 81.8% exhibited mucous glands; 41.7%, goblet cells; and 27.3%, argyrophil cells in the cyst wall. In 23 children, the incidence of these metaplastic changes was lower (27.3% mucous glands, 13.0% goblet cells, and 9.5% argyrophil cells). Immunoreactive-gastrin or -somatostatin was evident immunohistochemically in 4 adults.

Conclusion

Congenital choledochal cysts carry a risk of cancer, probably as a result of a sequence of pancreatobiliary reflux, inflammation, dysplasia with or without intestinal metaplasia, and invasive carcinoma. A combination of biliary stasis due to poor drainage of a stagnant pool of bile and increased mutagenicity of the bile acids may be ultimately responsible. The risk is low in childhood, but shows a clear increase with age. The implication for management is that total excision of the extrahepatic biliary tree at risk remains the gold standard for management of these cysts, and simple bypass in infancy or childhood leaves the risk of cancer, though possibly diminished, still significant.

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