

DOES THIS PATIENT HAVE CHOLEDOCHOLITHIASIS?

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The diagnostic challenge of choledocholithiasis can be attributed to the limited value of clinical symptoms, signs, and biochemical findings, and the number of investigative modalities. The most rewarding feature is the availability of minimally invasive treatment, making it possible to offer worthwhile treatment to patients of all age groups, including the most frail and elderly.

DEFINITION AND PREVALENCE

The term 'choledocholithiasis' best defines the presence of calculi in the common bile duct (CBD), as opposed to the more ambiguous generalisation 'gallstones' often used to refer to calculi situated either in the gallbladder or CBD. Calculi in both these locations have an age-related prevalence such that the 4.4%-12% prevalence of gallbladder calculi (i.e. cholelithiasis) in the age group 40-49 years increases to a prevalence of 15.2%-28.9% in the age group 70-79, according to post-mortem data.¹ Clinical surgical experience discloses a fivefold increase in the prevalence of choledocholithiasis when one compares the 71-80 age group with the 41-50 age group: 48% of patients undergoing cholecystectomy have stones.² Other parts of the biliary tract may harbour calculi: the designation 'hepatolithiasis' is reserved for those situated in intra- and/or extra-hepatic bile ducts.³ 'Mirizzi' syndrome signifies extrinsic compression of the common hepatic duct by a calculus impacted either in Hartmann's pouch or in the cystic duct.⁴

PATHOGENESIS

The majority of CBD calculi have migrated from the gallbladder;⁵ thus risk factors for choledocholithiasis (CDL) are the same as those for cholelithiasis, namely increasing age, female gender, childbearing, obesity, and ethnic origin (Scandinavian descent or native American descent).⁶ Biliary sludge might be a closely-related entity: synonyms such as 'microlithiasis', and 'pseudolithiasis' reflect uncertainty about whether or not this is a precursor to CDL.⁷ The factors which influence migration of calculi from the gallbladder to the CBD are poorly understood; one theory is that 1-4 mm diameter stones are the most likely to migrate, and that some increase in size within the CBD, thereby mediating an increase in back pressure, retrograde biliary distension, and an easier passage for larger stones to follow.⁵ Calculi which have migrated from the gallbladder to the CBD, are designated 'secondary' calculi; the term 'primary' calculi is reserved for those which originate within the CBD itself. The occurrence of CBD calculi in patients with agenesis of the gallbladder proves the potential for *de novo* formation at this site.⁸ Peri-ampullary diverticula may predispose to

the formation of primary CBD calculi.⁹ Those calculi which become symptomatic more than ten years after cholecystectomy are also more likely to be of 'primary' type in comparison with those which manifest themselves within the first three years post-operatively, the latter most probably being residual calculi overlooked at the time of the original operation.¹⁰ Stones in the CBD, regardless of aetiopathogenesis, predispose to acute pancreatitis,¹¹ the precise mechanism of which is not known. The hypothesis proposed by Opie is that a common channel sometimes exists between the pancreatic and common bile ducts, and thus allows bile to be diverted toward the pancreatic parenchyma in some patients with CDL, thereby initiating an inflammatory reaction in that organ.¹²

CLINICAL FEATURES

An asymptomatic clinical course characterises the majority of patients who either have cholelithiasis or choledocholithiasis: one estimate, derived from several sources, is that symptoms occur in only 10% of patients who harbour CBD calculi.¹³ A prospective evaluation of patients who required laparoscopic cholecystectomy, showed the following clinical findings were useful indicators of coexisting choledocholithiasis: jaundice (current, recent, or recurrent), light-coloured faeces/dark urine, pancreatitis (past or present), septic fever (present or recent). Their individual positive predictive values were 28.6%, 43.6%, 8.3%, and 36.4% respectively, for co-existing choledocholithiasis.¹⁴ Retrospective analysis of presenting features in 59 patients aged >75 years with proven choledocholithiasis revealed that jaundice, abdominal pain (on its own), and Charcot's triad (i.e. jaundice, biliary pain and pyrexia) occurred in 30%, 22%, and 12%, respectively, and that malaise, mental confusion, and failure to cope, occurred singly or in combination in up to 19% of patients.¹⁵ Eight per cent had an exclusively biochemical presentation, disclosed in the course of investigation of a totally unrelated illness.¹⁵ I analysed clinical features in 58 patients aged 65-99 years (41 of whom were female) over a period of 14.5 years; the prevalence of clinical findings was as follows: nausea and/or vomiting: 39.6% (including 'coffee grounds' vomiting in two patients, and concurrent diarrhoea in six others), abdominal pain 31%, abdominal tenderness: 13.7% with neither abdominal pain or backache, fever (present or recent) in 31% (including positive blood cultures for *E. coli* in 11 patients, i.e. 18.9% of the total), dark urine and/or pale stools in 20.6%, jaundice in only 10.3%, and hepatomegaly in 10.3%. Five percent reported acute pancreatitis and previous cholecystectomy, respectively, in one case cholecystectomy having been performed 40 years earlier. Non-specific symptoms were found: falls in 13.7%, weight loss in 12%, and malaise in 8.6%. One patient, admitted with angina, had subsequent investigation and validation of choledocholithiasis, following fortuitous documentation of an abnormal hepatic biochemical profile.

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BIOCHEMICAL ABNORMALITIES

In the context of risk factors such as increasing age and/or validated cholelithiasis, biochemical changes sometimes have a powerful positive predictive value. The serum bilirubin, alkaline phosphatase (ALP), gammaglutamyl transferase (GGT), 9 alanine transferase (ALT), and aspartate transaminase (AST) are usually assayed, with the first three significantly distinguishing (at the $p < 0.001$ to $p < 0.002$) between those patients who have coexisting CBD calculi and those who have neither calculi nor any other obstructive defects involving the CBD.¹⁶ In another analysis involving patients with proven cholelithiasis a positive predictive value of 63% for coexisting choledocholithiasis was obtained through the use of two or more abnormal liver function tests, including serum bilirubin, ALP, and ALT estimations.¹⁷ For individual liver function tests (upper reference limits in parentheses) in the context of validated cholelithiasis, positive predictive values for coexisting choledocholithiasis amounted to 57%, 53% and 49%, respectively for serum bilirubin of > 30 $\mu\text{mol/l}$ (17 $\mu\text{mol/l}$), ALP of > 300 iu/l (110 iu/l), and AST > 120 iu/l (40 iu/l).¹⁸ The predictive value of these biochemical parameters is enhanced further by taking age into account.^{16,18} In the presence of an intact gallbladder, if cholelithiasis cannot be detected by ultrasonography, or hepatobiliary dysfunction by biochemical profiling, the probability is virtually nil that the patient has choledocholithiasis.¹⁹ This assumption applies with greater force in the young than in the old, due to the age-related prevalence of this disorder.

DIFFERENTIAL DIAGNOSIS

Even with the benefit of liver function tests, differential diagnosis can be wide-ranging. The 'classical' combination of hyperbilirubinaemia and elevation of ALP to more than twice the upper reference limit (in conjunction with elevation of either GGT or ALT or AST) cannot always distinguish between extrahepatic biliary obstruction and intrahepatic bile stasis (including sepsis-related cholestasis),^{20,21} or between hepatic space-occupying lesions and diffusely infiltrative hepatic pathology.²⁰

Competing diagnoses are also age-related; for example, viral hepatitis A is more likely to be an alternative diagnosis in the young than in the old;²² the opposite holds true for carcinomatous biliary obstruction.²³ In conjunction with either cholelithiasis or choledocholithiasis, other biliary obstructive lesions may coexist, including primary biliary cirrhosis,²⁴ and primary sclerosing cholangitis,²⁵ respectively. Heart failure may also coexist, and also produces derangements in the hepatic biochemical profile.²⁶ When the resolution of hepatic biochemical derangements is incomplete following adequate treatment of heart failure, uncertainty remains about whether or not the residual hepatic dysfunction is due to coexisting choledocholithiasis.

A distinction also has to be attempted between remission in biochemical derangements which is attributable to spontaneous expulsion of a CBD calculus, and remission which occurs in spite of continuing retention of the calculus within the CBD. In the 58 patients analysed, the biochemical parameters which reverted to the normal in spite of continuing retention of the CBD calculus included serum bilirubin in 32.7% of cases, and serum ALP in 10%. This phenomenon also occurs with unresected ampullary carcinoma.²⁷

When serum ALP is elevated in the absence of

hyperbilirubinaemia, the diagnosis can either be choledocholithiasis²⁸ or involvement of the liver by a focal space-occupying, or diffusely infiltrative, lesion.²⁰

IMAGING MODALITIES

The simplest and most accessible of imaging modalities, plain radiography has the potential to document abnormalities such as pneumobilia (gas in the biliary tree), a feature of incompetence of the sphincter of Oddi,²⁹ sometimes complicating spontaneous expulsion of a CBD calculus, regardless of any retained CBD calculi.³⁰ More importantly, ultrasonographic imaging of the biliary tract, for confirmation or refutation of the provisional diagnosis of choledocholithiasis, cannot be successfully performed in the presence of pneumobilia.³¹

This caveat apart, ultrasonography retains wide appeal as the imaging modality of first choice, due to ease of accessibility, low cost, non-invasiveness, and freedom from radiation exposure. These advantages far outweigh such drawbacks as operator-dependent variability, poor technical quality in the presence of obesity or overlying bowel gas, and inability to visualise cholangiocarcinoma and ampullary carcinoma.³² Ultrasonography can also visualise hepatic space-occupying lesions such as liver abscess or tumours; these can then be verified by ultrasonographically-guided aspiration or biopsy. Sensitivity and specificity for identifying gallbladder calculi can be as high as 95%,³³ sensitivity is much lower for the detection of CBD calculi, varying from 25% to 82%.^{34,35}

Comparable diagnostic sensitivity for choledocholithiasis is achieved through computerised axial tomography,³² which can also clearly visualise retroperitoneal structures.³²

Because of inherent radiation exposure and greater expense, CT scanning should be limited to those patients with equivocal findings and those with difficult interpretation of the ultrasound scan.³²

Investigative strategies for detection of coexisting choledocholithiasis in candidates for laparoscopic cholecystectomy include preoperative endoscopic retrograde cholangiopancreatography (ERCP), intraoperative cholangiography via the cystic duct, or laparoscopic exploration of the CBD. The emerging consensus is that both intraoperative cholangiography and laparoscopic CBD exploration should be incorporated into the management strategy for laparoscopic cholecystectomy;³⁶ there is a consequent reduction in hospital stay, cost and morbidity, in comparison with sequential ERCP and laparoscopic cholecystectomy.^{37,38} The 'learning curve' is a steep one, both for laparoscopic cholecystectomy (characterised by a fivefold increase in procedure-related bile duct injury in comparison with 'open' cholecystectomy),^{39,40} and for laparoscopic CBD exploration, which has been described as 'technically demanding, and not in the usual armamentarium of many surgeons'.⁴¹ By comparison, ERCP, with percutaneous transhepatic cholangiography (PTC) as the alternative procedure, if the ampulla cannot be cannulated, is associated with a 90% success rate in accurately defining the site and nature of biliary obstruction and a 99% sensitivity and specificity in establishing the diagnosis of an extrahepatic obstructive process.³² PTC should be the preferred procedure in patients with 'surgically altered anatomy' and who do not have contraindications such as coagulopathy or ascites,³² but this advantage is offset by the technical difficulty in gaining access to non-dilated

ducts associated with a reduced success rate to 70%.³² Patients belonging to the latter category should be preferentially managed by ERCP, notwithstanding the observation that procedure-related acute pancreatitis is more likely to occur when bile ducts are non-dilated than when they are dilated.⁴² This complication is clinically significant in only 2.0-5.4% of patients undergoing ERCP.^{43,44} Other complications, including those attributable to the adjunctive use of endoscopic sphincterotomy, comprise haemorrhage (2-4%), perforation (1%),^{43,44} cholangitis (1%)⁴² and a 0.6-0.7% procedure-related mortality.⁴³ A minimal risk exists of failure to detect stones of < 3.0 mm diameter which are situated in a dilated CBD.⁴⁵

A more recently introduced investigation is endoscopic ultrasonography (EUS), which utilises a high-frequency ultrasound probe to visualise the entire extrahepatic biliary tree; this modality is virtually indistinguishable from ERCP in terms of sensitivity, specificity, and positive predictive value for detection of CBD calculi.⁴⁶ Small calculi, situated within a dilated CBD, may also escape detection by EUS.⁴⁶ Specificity may occasionally fail: CBD calculi were indicated by ERCP in two patients, and by EUS in one patient and, on subsequent choledocholithotomy, no stones were found.⁴⁷ Both procedures may be poorly tolerated by some patients, and recourse to EUS may be useful when cannulation of the ampulla fails during attempted ERCP.⁴⁷

In comparison with spiral computed tomography (spiral CT), in which the imaging principle is that of rapid acquisition of three-dimensional data, EUS proved to be the more sensitive modality in the course of evaluation of suspected malignant biliary obstruction. It was particularly useful in the visualisation of small ampullary or pancreatic tumours missed by spiral CT.⁴⁸ Magnetic resonance cholangiography (MRC) is the latest arrival on the diagnostic scene, utilising three-dimensional fast spin technology with respiratory gating - although the latter failed to achieve satisfactory reduction in movement artefact in 4.3% of the subjects enrolled in one of their studies.⁴⁹ Seven subjects with intraductal filling defects, MRC and ERCP achieved comparable sensitivity for detection of CBD calculi, and both misidentified a ductal polyp as a calculus.⁴⁹

A resurgence of interest has occurred in intravenous cholangiography, principally in order to circumvent technical difficulties and prolongation of operating time associated with operative cholangiography, and also to avoid the expense, morbidity, and mortality associated with pre-operative ERCP. When administered by slow intravenous infusion, the newer contrast agent, meglumine iotroxate, is reportedly associated with fewer adverse reactions than the older contrast agent, iodopamide. It has yielded sensitivities and specificities of 89% and 99% respectively, in comparison with the 'gold standard', ERCP, for diagnosis of biliary obstruction.⁵⁰ Unlike ERCP or PTC these imaging modalities do not confer adjunctive therapeutic strategies. For example, during ERCP, the adjunctive use of either endoscopic sphincterotomy or endoscopic balloon dilatation,⁵¹ enables both diagnosis and treatment to be accomplished at the same sitting, and a calculus which is too large to be expelled by either procedure can be crushed by mechanical lithotripsy,⁵² electrohydraulic lithotripsy (using a high voltage discharge),⁵³ or by laser technology, access to the CBD having been obtained via a 'mother and baby' scope.^{53,54} If endoscopic cannulation of the ampulla proves difficult due to anatomical variations, PTC can be

utilised for extraction of the CBI calculus with a potential 93% success rate.⁵⁵ The procedure which has not gained enthusiastic acceptance is intraductal contact dissolution, as it is tedious and associated with gastrointestinal side-effects.⁵⁶ If the CBD calculus can neither be extracted nor crushed into sufficiently small fragments, recourse to biliary endoprosthesis is the most viable therapeutic alternative, especially in those with cholangitis.⁵⁷ A cohort of patients aged 77-97 years has now been followed up for 28-78 months; these demonstrate freedom from biliary symptoms. Death was from unrelated illnesses in 20 out of 23 instances after this procedure.⁵⁸ Long-term follow-up in 115 patients aged under 60, who underwent ERCP and 'standard' endoscopic sphincterotomy (without endoprosthesis) was used to evaluate long-term sequelae of the procedure.⁵⁹ Long-term information was available in 103 patients followed up for 10.4-19.3 years; complications were recorded in 9.7% (i.e. ten patients), comprising acute cholangitis in five, four of whom had recurrence of CBD calculi and the fifth patient had a stenosed papilla without associated choledocholithiasis. Another four patients experienced recurrence of choledocholithiasis without associated cholangitis. In one other patient, the only biliary complication was acute cholecystitis.⁵⁹

CONCLUSION

Technological advances have widened the spectrum of diagnostic and therapeutic modalities for choledocholithiasis, thereby enabling more precise patient management. Nevertheless, the truism is still as valid today as it was in 1989 that 'despite the extensive array of new techniques available to examine patients who have jaundice - or because of it - the CE (i.e. clinical examination), including the initial history, physical examination, basic laboratory tests, and serological studies, remains the most important diagnostic modality.'³²

Teaching points:

- **Given the limited ability of ultrasonography to detect common bile duct calculi, the association of ultrasonographically validated cholelithiasis and any derangement of the hepatic biochemical profile can be utilised as an alternative strategy to predict ERCP validation of choledocholithiasis.**
- **Spontaneous improvement in the hepatic biochemical profile can occur to the same extent either in spite of continuing retention of the CBD calculus, or as a result of its spontaneous expulsion.**
- **ERCP, with adjunctive sphincterotomy (and other interventional procedures) presently constitutes the best strategy for optimising management of choledocholithiasis.**

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