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CLINICAL STUDY

Consideration of endoscopic retrograde cholangiopancreatography in cases of acute biliary pancreatitis

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Abstract: *Aim:* The important question to be answered in all cases of ABP is whether or not a calculous biliary obstruction is still present. Answering this question conditions subsequent management, including the need for endoscopic retrograde cholangiopancreatography (ERCP). The aim of this study was to determine the relationship between persistent common bile duct stone (CBDS) and laboratory values, and dilation of bile duct in order to find possible significant associations in patients with acute biliary pancreatitis (ABP).
Methods: Retrospectively, statistical evaluation of a group of 76 patients with ABP who had received early ERCP.
Results: The prevalence of choledocholithiasis in patients >70 years old was 54.2 %, in patients ≤70 years old it was 36.5 %. Following cholecystectomy, CBDS was present in 81.8 % of patients, p=0.005. The probability of CBDS occurrence in patients >70 years old with bile duct dilation was 81.3 %; in the absence of bile duct dilation CBDS was not present, p<0.001. The probability of CBDS occurrence in patients 70 years old with bile duct dilation was 57.7 %, in the absence of bile duct dilation CBDS was present in 15.4 %, p=0.002. In patients with bile duct dilation predictive factors are as follows: bilirubin (Bi), after excluding patients with acute cholecystitis and cholangitis, p=0.05; alanine aminotransferase (ALT) in patients 70 years old, p=0.004; gamma-glutamyl transferase (GMT) in patients >70 years old, p=0.02.
Conclusions: ERCP is indicated in patients with ABP if biliary obstruction is present and the presence of a ductal stone is suspected. From our results it is clear that the predictive parameter for choledocholithiasis is the dilation of the bile duct and previous cholecystectomy. In patients with bile duct dilation possible predictive factors are Bi, ALT, and GMT *(Tab. 1, Fig. 8, Ref. 20)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: acute biliary pancreatitis, endoscopic retrograde cholangiopancreatography.

Gallstone migration through the biliary tract can cause acute pancreatitis (1). The exact means by which gallstones cause pancreatitis has remained incompletely understood, although transient obstruction of the pancreatic duct appears to play a major role (2). In many cases biliopancreatic obstruction is transient because the offending stone passes rapidly into the duodenum; in the remainder, persisting obstruction occurs due to the continued presence of a main bile duct stone or to ampullary edema following stone passage (3). Biliary pancreatitis can be presumed when abdominal ultrasonography (USG) confirms gallbladder or bile duct stones and, in particular, when serum hepatic transaminases are acutely increased in the initial presentation, and alcohol is reliably excluded (4). Early therapeutic endoscopic retrograde cholangiopancreatography (ERCP) reduces complications among acute pancreatitis patients who have biliary obstruction (5, 6). Because stones have a propensity to move spontaneously from the bile duct, the important question to be answered in all cases of ABP is whether or not a calculous biliary obstruction is still present. Answering this question conditions subsequent management, including the need for ERCP and endoscopic papillosphincterotomy (EPS) or surgical procedures, intraoperative cholangiography (IOC), choledochotomy or non-invasive tests, magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasonography (EUS) (6). Employing non-invasive, widely used and readily available tests, we endeavoured to establish predictive criteria, which would predict the presence of CBDS in patients with ABP with the highest probability.

Methods

The goal of this paper is to examine in patients with ABP the relationships between persistent CBDS and their laboratory value parameters, and with dilation of their bile duct to find significant associations. Acute pancreatitis was considered as biliary if on the first examination the serum amylase was >4 reference

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value (N) and if at least one of the following abnormalities was present: serum transaminases >3N, jaundice, cholangitis, cholecystolithiasis or dilated common bile duct upon USG examination (2). A group of 76 consecutive patients with ABP who had received early ERCP (within 48 hours) at the time when there was no possibility to perform MRCP and EUS regularly, was retrospectively evaluated. The following factors were studied: age, dilation of the common bile duct, and laboratory parameters, specifically Bi, ALT, which had been done in all patients prior to ERCP, as well as GMT, aspartate aminotransferase (AST), and alkaline phosphatase (ALP). Pathologic laboratory values were considered to be values higher than the reference values: Bi>22.2 μmol/l, AST>0.66 μkat/l, ALT>0.66 μkat/l, GMT >0.82 μkat/l, ALP>2.6 μkat/l, AMS>3.7 μkat/l. All biochemical parameters were estimated using the ADVIA 1640 analyzer (Siemens Healthcare, Germany). The presence of CBDS and the common bile duct diameter were determined by ERCP, or by IOC in patients where ERCP was unsuccessful (4 patients). In ERCP the bile duct was considered dilated when the diameter was 10 mm or more. Prior to ERCP ultrasound was employed to determine the common bile duct diameter. With ultrasonography, the bile duct was considered dilated when the diameter was more than 7 mm (9 mm and more after cholecystectomy).

The patient group consisted of 76 patients, age 24 to 92 years, 20 males, and 56 women. Due to retrospective nature of these evaluations, severity of pancreatitis was determined by the clinical course, and CT severity index (Balthazar's classification) (7).

Statistical methods

The associations between the presence of CBDS and bile duct dilation, and changes in laboratory parameters were investigated by dividing patients into two sub samples: with CBDS and without CBDS.

Their quantitative data (values of laboratory parameters, width of common bile duct) were compared using Student's *t*-test. Using Relative Operating Characteristic (ROC) curve, the cut-off value for each significant variable on the *t*-test as a multiple of the normal value of the relevant parameter was determined. Thus two categorical variables were obtained, which were compared by the chí^2 test of independence, and logistic regression.

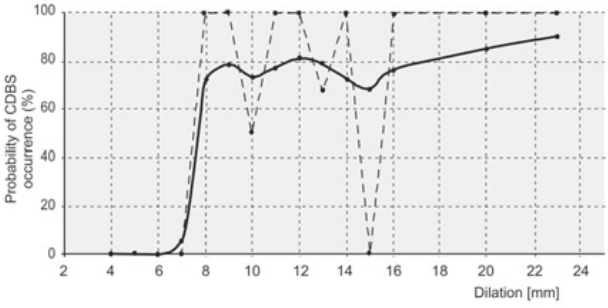

Fig. 1. Relationship between CBDS occurrence and bile duct dilation; age >70 years

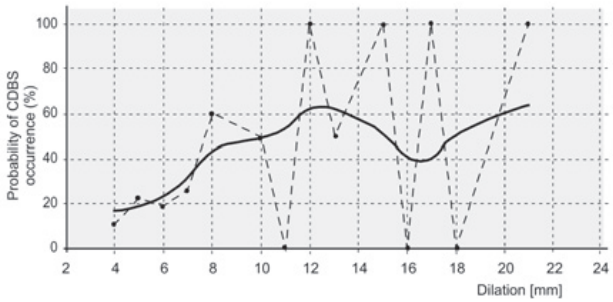

Fig. 2. Relationship between CBDS occurrence and bile duct dilation; age ≤70 years.

For small groups of patients Fisher's exact test was used; logit confidence intervals for the odds ratio was calculated using the method of Alan Agresti (8).

Results

USG findings: Before employing ERCP the common bile duct diameter was determined using ultrasound. The dilation of bile duct was accurately defined by ultrasound in 72.4 % (55/76) of our patients.

The gallbladder was also examined using ultrasound. Cholecystolithiasis was present on USG in 75.0 % of the patients (57/76), sludge in 2.6 % (2/76). There was no cholecystolithiasis in 7.9 % (6/76) patients; and, 14.5 % (11/76) of the patients had previously had cholecystectomy. CBDS was found on USG in 9.2 % (7/76) of the patients.

ERCP findings: Bile duct cannulation was successful in 94.8 % (72/76) of our patients, in 22.4 % (17/76) after previously pre-cut papillotomy. ERCP was not successful in 5.3 % (4/76) of the patients. CBDS was present upon ERCP investigation in 40.8 % of the patients (31/76); 29.0 % (9/31) of them were impacted. In one patient with unsuccessful ERCP, IOC revealed a stone in the common bile duct. In total CBDS was present in 42.1 % (32 patients). Bile duct dilatation was present according to ERCP in 51.3 % of the patients (39/76); bile ducts were not dilated in 43.4 % (33/76). In 3 patients, with whom ERCP was unsuccessful, the bile duct dilation was found on IOC. Bile duct dilation was present in a total of 55.3 % (42/76) of our patients.

Endoscopic extraction of common bile duct stones was successful in 87.5 % (28/32) of our ABP patients with CBDS present; surgery was recommended to 12.5 % of the patients (4/32) (one patient with unsuccessful ERCP involved). One patient who underwent surgery for unsuccessful stone extraction had also hemodynamically significant bleeding after EPS. EPS was also performed on 36.4 % (16/44) patients without CBDS occurrence.

Inflammatory complications of the gallbladder and bile ducts in ABP: Of the 76-patient group, 21 % (16/76) had acute cholecystitis, which was confirmed surgically. In 25 % (4/16) of these patients CBDS was present. All of the patients with both acute cholecystitis and CBDS occurrence had acute cholangitis simultaneously; all had EPS and stone extraction performed. 50 % of

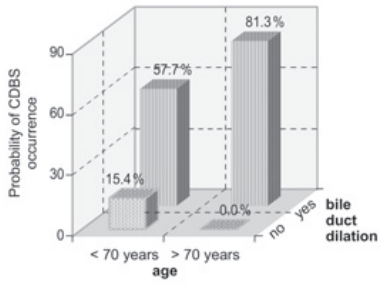

Fig. 3. Relationship between CBDS occurrence and age as well as bile duct dilation.

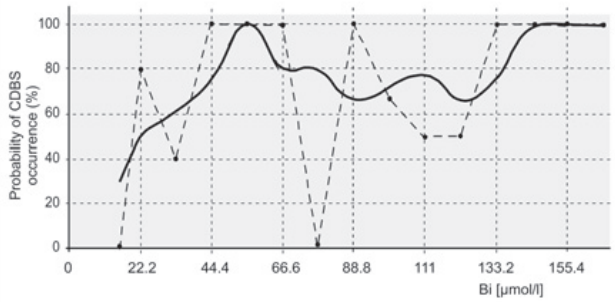

Fig. 4. Relationship between CBDS occurrence and bilirubin level in patients with bile duct dilation, without acute cholecystitis.

the patients with acute cholecystitis in our patients group were >70 years old; 25 % were diabetics.

Patients with previous cholecystectomy: ERCP was performed in 11 patients with ABP who had previously undergone cholecystectomy. Ten were female, 1 was male; the age range was 44 to 80 years with a mean age of 63.8±8.6 years. One patient underwent ERCP for onset of ABP 12 days after cholecystectomy; the bile duct was not dilated, two grain-like bile duct stones were present. EPS and stone extraction were successful. Ten patients had ABP attacks and underwent ERCP 3 to 14 years after cholecystectomy; all had bile duct dilation, 8 had CBDS, 6 of them had multiple stones. EPS and stone extraction were successful in 6 patients, two underwent surgery. None of these patients had cholangitis.

Statistical data processing

The prevalence of CBDS across the patient group with ABP was 42.1 % (32/76); bile duct dilation was present in 55.3 % (42/76).

Following cholecystectomy (11 patients), CBDS was present in 81.8 % (9/11), p=0.005.

Severe pancreatitis was diagnosed in 15.8 % (12/76) and mild pancreatitis in 84.2 % (64/76) of the patients. CBDS was present in 16.7 % (2/12) of the patients with severe pancreatitis and in 46.9 % (30/64) of the patients with mild pancreatitis, p=0.05.

Because the prevalence of choledocholithiasis increases with age (6), the group of patients was divided into two subgroups: 1. Age >70 years (24 patients, mean age 78.3±5.9 years), 2. Age ≤70 years (52 patients, mean age 51.8±12.1 years).

The prevalence of CBDS in patients >70 years old with ABP was 54.2 % (13/24); in patients ≤70 years old it was 36.5 % (19/52).

The associations between CBDS occurrence and bile duct dilation, and biochemical parameters

Bile duct dilation: The probability of a stone being present in the bile duct in patients >70 years old if the bile duct is dilated was 81.3 % (13/16); in the absence of bile duct dilation in patients >70 years old, CBDS was not present, p<0.001 (Figs 1 and 3). The probability of CBDS in patients ≤70 years old, if the bile duct is dilated was 57.7 % (15/26); in the absence of bile duct dilation in patients ≤70 years old the probability of CBDS was 15.4 % (4/26), p=0.002 (Figs 2 and 3).

Bilirubin: Excluding patients with concomitant acute cholecystitis, a significant association was found between CBDS and bilirubin level across the patient group, not divided by age, with dilated bile duct. The probability of CBDS occurrence for bilirubin level >1.5N is 81.8 % (18/22) and for bilirubin level <1.5N is 50 % (6/12), p=0.05 (Fig. 4).

In patients ≤70 years old with neither acute cholecystitis nor dilated bile duct we found an association between CBDS occurrence and bilirubin level together with ALT activity. For Bi>1.5N occurring with an ALT>8N CBDS is present in 33.3 % (4/12) and in 0% (0/9) for Bi<1.5N or ALT<8N, not significant (NS), p=0.08 (Fig. 5).

ALT: We found a statistically significant association between CBDS occurrence and ALT activity only after dividing the patient group into two subgroups according the age. In patients ≤70 years old with dilated bile duct and 3N<ALT<7N or ALT>12N, CBDS was present in 81.3 % (13/16) and in 20 % (2/10) for other ALT values, p=0.004 (Fig. 6). In patients with bile duct dilation and CBDS we found ALT activity to be dependent on age. The median ALT activity for these patients <50 years old was 10.6 µkat/l and for patients ≥50 years old the median of ALT was 2.9 µkat/l. The difference in mean ALT activity is sta-

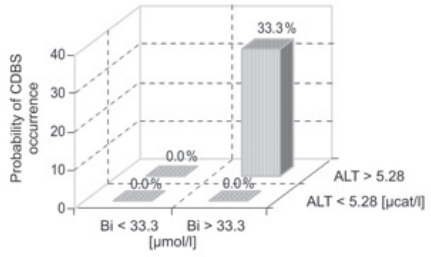

Fig. 5. Relationship between CBDS occurrence and Bi level as well as ALT activity; without bile duct dilation, without acute cholecystitis, age ≤70 years.

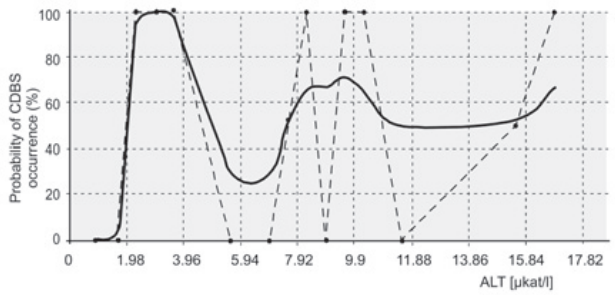

Fig. 6. Relationship between CBDS occurrence and ALT activity; age ≤70 years, with bile duct dilation.

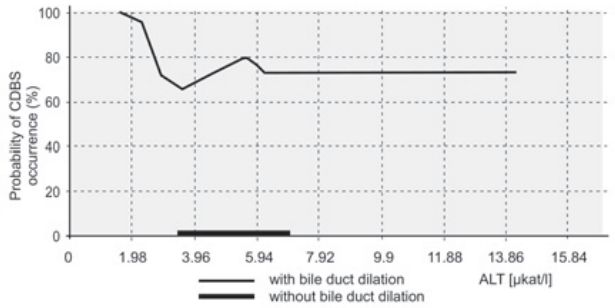

Fig. 7. Relationship between CBDS occurrence and ALT activity; age >70 years.

tistically significant, p = 0.05. We did not find a statistically significant association between the ALT activity and CBDS occurrence in patients >70 years old. But, all patients with dilated bile duct accompanied by ALT<3N had CBDS (Fig. 7).

GMT: CBDS was present in 100% (8/8) of patients >70 years old who had a dilated bile duct and GMT>5N and in 25 % (1/4) with GMT<5N, p = 0.02 (Fig. 8). We did not find a statistically significant association between the GMT activity and CBDS occurrence in patients ≤70 years old; but, not everybody in this patient subgroup had the GMT activity examined prior to ERCP.

Table 1 summarizes the CBDS predictors for patients with ABP.

Discussion

Although ABP is a common clinical problem, an optimal management is not entirely clear (9). ERCP is used selectively in ABP because it is difficult and has the potential of causing further pancreatic damage (9). As mentioned in the literature, persistent bile duct stones are found in 45 % to 70 % of patients with ABP when evaluated acutely and in 15 % to 30 % after resolution of symptoms, suggesting that emergency efforts and clearing stones from the duct or the ampulla may influence the course of the disease. Presumably, clearance of an impacted stone and prevention of recurrent impaction by additional stones limit pancreatic injury (4).

In our patient group ERCP was performed within 48 hours after admission for ABP. We found residual CBDS in 42.1 % of patients with ABP. When we divided the patients group by age into two subgroups, CBDS was present in 36.5 % of patients 70 years old and in 54.2 % of patients >70 years old (the difference is not statistically significant, p=0.15). Due to the retrospective nature of our evaluation, severity of pancreatitis in our patient group was determined by the clinical course (Atlanta classification) and CT findings (Balthazar's classification) (7). CBDS was more frequent in patients with mild ABP (46.8 %) than in those with severe ABP (16.7 %), p=0.05. Other studies, too, showed no relationship between disease severity and the presence of CBDS (10). It is not always possible to determine the severity of pancreatitis in the first hours after the onset of ABP. Commonly used scales (Ranson's, Glasgow criteria) used readily available clinical data to predict prognosis in acute pancreatitis, but were not specifically meant to select patients for ERCP or to identify patients with biliary obstruction (5). The decision to perform ERCP should be based on the results of simple emergency tests. Using ultrasonography, which allows the measurement of bile duct diameter, in combination with biochemical and clinical parameters, it is possible to categorize patients according to the likelihood of CBDS (6). These parameters reflect the presence of biliary obstruction regardless of pancreatitis severity.

Statistical analysis of these parameters in our patient group having ABP, provided the following results: bile duct dilation, and previous cholecystectomy at any time in the past, is an important predictive factor at any age. The significance of the dependence between CBDS occurrence and bile duct dilation increases with the age; patients >70 years old did not have choledocholithiasis without bile duct dilation. In patients ≤70 years old CBDS was also present in patients without bile duct dilation (in 15.4 % of patients).

In the subgroup of patients following cholecystectomy, in one patient, who had undergone recent cholecystectomy, pancreatitis onset was probably caused due to operative spilling of the stone into common bile duct. In the other ten patients ABP was probably caused by retained or recurrent common bile duct stones.

Bilirubin and ALT were tested for every patient before ERCP. Bilirubin level was influenced by the presence of acute cholecystitis, which was surgically verified in 21 % of the patient study

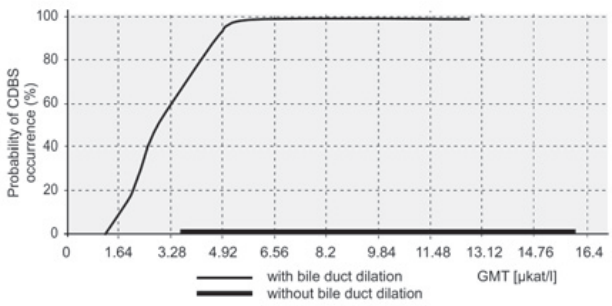

Fig. 8. Relationship between CBDS occurrence and GMT activity; age >70 years.

Tab. 1. CBDS predictors for patients with ABP.

Patients	Predictor	% CBDS	Odds ratio (95% CI[1])	p value
entire group	following cholecystectomy	81.8	8.0 (3.5 to 18.2)	0.005
without acute cholecystitis with bile duct dilation	Bi>1.5N	81.8	4.2 (0.9 to18.3)	0.05
age >70 years	bile duct dilation	81.3	87.4 (14.4 to 528.8)	<0.001
age >70 years with bile duct dilation	GMT>5N	100.0	57.6 (7.6 to 435.4)	0.02
age ≤70 years	bile duct dilation	57.7	7.5 (2.0 to 28.1)	0.002
age ≤70 years with bile duct dilation	3N<ALT<7N or 12N<ALT	81.3	17.3 (5.2 to 34.0)	0.004

[1] – confidence interval

group and by the presence of acute cholangitis found in 5.3 % of the patients (all patients with acute cholangitis also had acute cholecystitis). Even without detectable common bile duct obstruction, acute cholecystitis often causes mild elevations in the serum aminotransaminase, alkaline phosphatase levels and serum bilirubin concentrations (11). The elevated bilirubin level in patients with acute cholecystitis may be a consequence of haemathogenous or direct spread of infection, which may cause structural and functional abnormalities of the liver (13). The clinical course of acute cholecystitis in some patients (diabetics, advanced age) may be masked, and the inflammatory process on the gallbladder may have a rapid course with the development of gangrene (14). Also in ABP there is difficult to exclude the diagnosis of acute cholangitis (15), and cholecystitis because the clinical symptoms, and laboratory parameters may be overlapped by the presence of acute pancreatitis. According to our experiences elevated bilirubin levels in patients without CBDS upon ERCP for acute biliary pancreatitis or after successful endoscopic extraction of CBDS may draw attention to the development of acute cholecystitis. Cholecystitis itself may also be a consequence of ERCP and common bile duct stone removal (15).

Since the patients in our group with acute cholecystitis had elevated bilirubin levels even when CBDS was not present, the relationship between bilirubin level and CBDS was significant (p=0.05) in patients with bile duct dilation after elimination of patients with acute cholecystitis only. Other authors found total serum bilirubin level to be the best clinical predictor of persistent CBDS (12). In patients without bile duct dilation we did not find, even after elimination of patients with acute cholecystitis, a simple correlation between CBDS and bilirubin level. Occurrence of CBDS was related to bilirubin level in combination with ALT activity (NS, p= 0.08).

In patients ≤70 years old with dilated bile duct, another predictive factor was an ALT activity, p=0.004. We found the age to be a factor influencing ALT activity in patients with CBDS and bile duct dilation. Younger patients with dilated bile duct and CBDS had higher ALT activity; older patients with CBDS also had elevated ALT activity, but of a lesser degree than the younger patients. A significant correlation between serum ALT activity and age was found in individuals without liver diseases (16, 17). We suppose that a similar correlation may occur in patients with hepatobiliary diseases. Two intervals of ALT values, as predictors of residual CBDS, are probably the result of age-dependent ALT activity and eventually the spontaneous movement of the stones (Fig. 6). We did not find a statistically significant association between the ALT activity and CBDS occurrence in patients >70 years old; but, all those patients with dilated bile duct accompanied by an ALT <3N had CBDS, it means that old patients may have CBDS with slightly increased ALT values.

Although not all of our patients had a GMT activity done prior to ERCP, for patients >70 years old, with bile duct dilation, the most important predictive biochemical factor was GMT.

ERCP is indicated in patients with suspected ABP if persisting biliary obstruction is present and the presence of ductal stone is suspected. If the predictive factors of biliary obstruction are not present, or the symptoms are improving and the laboratory parameters are decreasing in a period of few hours, which suggests a spontaneous stone passage, it is useful to perform a less invasive or non-invasive investigation of the bile ducts (EUS, MRCP); ERCP and subsequent EPS is indicated only if the presence of CBDS is confirmed by these methods (4, 10). The limitation of EUS includes availability and operator dependence. The limitations of MRCP include variable quality, difficulty in performing this procedure in critically ill or uncooperative patients, and contraindications. Sensitivity of MRCP for small bile duct stones is lower, especially for those that are impacted at the ampulla (18). Indeed, ERCP offers the opportunity to perform EPS when indicated for CBDS presence as well as in patients with ABP without CBDS (insufficient biliary drainage due to ampullary edema, reducing the risk of recurrent pancreatitis in patients with cholecystolithiasis in older and high surgical risk patients) (19, 20).

Our results clearly demonstrate that the definitive predictive parameters for CBDS in ABP patients are bile duct dilation, and previous cholecystectomy at any time in the past; the significance of dilation increases with age. In patients with bile duct dilation, a possible predictive factors are bilirubin levels, providing that acute cholecystitis and cholangitis are not present. ALT activity is a predictive factor, however, it is infuenced by age; and GMT is also predictive, but in our study primarily in older patients as not all patients had undergone GMT testing before ERCP.

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