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DETERMINATION OF PREDICTIVE FACTORS OF CHOLEDOCHOLITHIASIS IN CASES OF ACUTE BILIARY PANCREATITIS

Cholelithiasis (bile duct stones) may bring about biliopancreatic obstruction that eventually develops into acute biliary pancreatitis, which could become a serious, life threatening disease. Because stones have the propensity to move spontaneously from the bile duct, it is all-important to determine as accurately as possible, whether biliopancreatic obstruction is still present or not. The aim is to avoid, wherever possible, any invasive and costly diagnostic and therapeutic procedures while preventing serious risk to the patient. In this paper, by retrospective analysis of patients with acute biliary pancreatitis, we examine laboratory and other parameters, obtained by quick and easy to implement non-invasive methods, for to determine predictive factors of biliopancreatic obstruction. Our results indicate that the definite predictive parameter for choledocholithiasis is previous cholecystectomy and the dilation of the bile duct. Supporting predictive factors are bilirubin and alanine aminotransferase.

Key words: acute biliary pancreatitis, endoscopic retrograde cholangiopancreatography, Chi-square tests.

Abbreviations: ABP, acute biliary pancreatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Bi, bilirubin; CBDS, common bile duct stone; EPS, endoscopic papillosphincterotomy; ERCP, Endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; GMT, gamma-glutamyl transferase; IOC, intraoperative cholangiography; MRCP, magnetic resonance cholangiopancreatography; N, reference value; NS, not significant; ROC, Relative Operating Characteristic; USG, ultrasonography.

1. Introduction

Gallstone (cholelithiasis) disease is a very common condition involving roughly 15% of the population in Europe. In 10% to 15% of cases, cholelithiasis is complicated by the presence of common bile duct stones. Gallstone migration through the biliary tract can cause acute pancreatitis [1]. In many cases biliopancreatic obstruction is transient because the offending stone passes rapidly into the duodenum; otherwise persisting obstruction occurs due to the continued presence of a main bile duct stone or to ampullary edema following stone passage [2]. Biliary pancreatitis can be presumed when abdominal 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 [3]. Early therapeutic ERCP reduces complications among acute pancreatitis patients who have biliary obstruction [1, 4]. 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 EPS or surgical procedures, IOC, choledochotomy or non-invasive tests, MRCP, and EUS [1]. Employing non-invasive, widely used and readily available tests, we endeavoured to establish

predictive factors-predictors, which would predict the presence of common bile duct stone in patients with ABP with the highest probability.

2. Patients and methods

Our aim was to examine in patients with ABP the relationships between persistent CBDS and values of their laboratory parameters, and with dilation of their bile duct to find significant associations.

For this purpose we retrospectively, in two stages, statistically evaluated the database of total 130 consecutive patients with ABP referred from Martin Faculty Hospital, Internal Gastroenterology Clinic, Martin, Slovakia in the years 1999–2008.

Stage 1. Patients from 1999 to 2003, had received early ERCP (within 48 hours) at the time when we had not had the possibility to perform MRCP and EUS regularly. These patients, group I, $n = 76$, (20 men and 56 women) mean age 60.1 ± 16.3 years (range 24 - 92) were used to determine predictors for CBDS. Analysis was performed on the whole group.

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We studied following factors: age, dilation of the common bile duct, and laboratory parameters, specifically Bi, ALT, which had been done to all the patients prior to ERCP, as well as GMT, AST, ALP and dependence of CBDS occurrence from previous cholecystectomy. Pathologic laboratory values were considered to be higher than the reference values (N): $Bi > 22.2 \mu\text{mol/l}$, $AST > 0.66 \mu\text{kat/l}$, $ALT > 0.66 \mu\text{kat/l}$, $GMT > 0.82 \mu\text{kat/l}$, $ALP > 2.6 \mu\text{kat/l}$, $AMS > 3.7 \mu\text{kat/l}$. The presence of CBDS and the common bile duct diameter were determined by ERCP or by IOC in patients where ERCP was unsuccessful. In ERCP we considered the bile duct dilated when the diameter was 10 mm or more. Prior to ERCP we employed ultrasound to determine the common bile duct diameter. With ultrasonography, we considered the bile duct dilated when the diameter was more than 7 mm (9 mm and more after cholecystectomy).

The associations between the presence of CBDS and bile duct dilation or the values above the mentioned laboratory parameters or previous cholecystectomy were investigated by dividing patients into two sub groups: with CBDS and without CBDS. Their quantitative data (values of laboratory parameters) were compared using Student's *t*-test. For each significant variable on the *t*-test, using ROC curve, we determined the cut-off value as a multiple of the normal value of the relevant parameter. Thus we obtained two categorical variables, which were compared by the χ^2 test of independence, and logistic regression. Using χ^2 test of independence we also investigated the association between occurrence of CBDS and dilation of common bile duct or previous cholecystectomy. For small groups of patients we used Fisher's exact test; logit confidence intervals for the odds ratio was calculated using the method of Alan Agresti [5]. We considered *p*-values ≤ 0.05 as statistically significant.

Because the prevalence of choledocholithiasis increases with age, [1], and an interaction appeared between the age and other predictors, the multivariate analysis was performed separately for patients older and younger than 70 years.

3. Results

The prevalence of choledocholithiasis in patients ≤ 70 years old with ABP (52 patients, mean age 51.8 ± 12.1 years) was 36.5% (19/52), in patients > 70 years old (24 patients, mean age 78.3 ± 5.9 years) was 54.2% (13/24).

We determined the following significant associations:

Bile ducts dilation. The probability of the presence of a stone in the bile ducts if the bile ducts are dilated was 66.7% (28/42), in the absence of bile duct dilation the probability of CBDS occurrence was 11.7% (4/34), sensitivity 87.5%, specificity 68.2%, $p < 0.001$.

Bilirubin. Bilirubin is examined on all patients with ABP. We did not find a statistically significant association between the Bi level and CBDS occurrence even after dividing patients by age. Therefore, we explicated some other medical factors, which could

have influenced the value of Bi, hence adversely affected achievement while determining the association between persisting CBDS and increased level of Bi. It was established that if we from the tested group of patients excluded all these with acute cholecystitis and cholangitis (diagnoses with increased value of Bi) a significant association would exist between the CBDS occurrence and bilirubin level in the whole patients group, not divided by age, with dilated bile ducts. 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). Sensitivity 75%, specificity 60%, $p = 0.05$.

ALT. We found a statistically significant association between CBDS occurrence and ALT activity only after dividing the whole patients group into two subgroups according to their age. In patients ≤ 70 years old with dilated bile ducts and $3N < ALT < 7N$ or $ALT > 12N$ CBDS is present in 81.3% (13/16) and in 20% (2/10) for other values of ALT. Sensitivity 86.7%, specificity 72.7%, $p < 0.004$.

For the patients ≤ 70 years old without acute cholecystitis with not dilated bile ducts we found an association between the 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 $ALT < 8N$. Sensitivity 100%, specificity 52.9%, $p = 0.08$ (NS).

As for patients with bile ducts dilation with CBDS occurrence we found the dependence of ALT activity on age. The median of ALT for these patients ≤ 50 years old is $10.6 \mu\text{kat/l}$ and for patients > 50 years old median of ALT is $2.9 \mu\text{kat/l}$. The mean difference is statistically significant, $p < 0.05$.

We did not find a statistically significant association between the ALT activity and CBDS occurrence at patients > 70 years old. Even patients with dilated bile ducts had CBDS also in the case of $ALT < 3N$, while $ALT > 3N$ is one of symptoms by ABP.

GMT. A bile duct stone is present in 100% (8/8) of patients > 70 years old with dilated bile ducts and $GMT > 5N$, and in 25% (1/4) with $GMT < 5N$ and with dilated bile ducts.

Sensitivity 88.9%, specificity 100%, $p = 0.02$.

We did not find a statistically significant association between the GMT activity and CBDS occurrence at patients ≤ 70 years old; but, not everybody in this group had GMT examined before ERCP.

Previous cholecystectomy. By patients with previous cholecystectomy CBDS was present in 81.8% (9/11). Sensitivity 28.1%, specificity 95.5%, $p = 0.005$.

Stage 2. The results we obtained by studying the associations between CBDS and laboratory parameters, previous cholecystectomy, [6], and dilated bile duct on the group I, were verified on the control group of patients with ABP treated in the MNF hospital in Martin in the years 2004–8, group II, which consisted of 54 patients (19 men and 34 women) mean age 63.5 ± 16.3 years (range

CBDS significant predictors for patients with ABP

Table 1

Patients	Predictor	% CBDS	Odds ratio (95% CI)	pValue
entire group	previous cholecystectomy	81.8	8.0 (3.5 to 18.2)	0.005
entire group	bile duct dilation	66.7	15.0 (4.5 to 48.8)	< 0.001
without acute cholecystitis with bile duct dilation	Bi > 1.5N	81.8	4.2 (0.9 to 18.3)	0.05
age ≤ 70 years with bile duct dilation	3N < ALT < 7N or 12N < ALT	81.3	17.3 (5.2 to 34.0)	0.004
age > 70 years with bile duct dilation	GMT > 5N	100	57.6 (7.6 to 435.4)	0.002

24–86). By using *t*-test, and χ^2 - “goodness of fit” test, respectively, we found that the difference in age composition in both groups I and II, and the difference between observed and expected probabilities of CBDS occurrence depending on bile duct dilation, values of ALT, Bi and previous cholecystectomy in the group II, resp., is not significant. The value of test criteria χ^2 equals $1.041 < \chi^2_{0.05}(3) = 7.81$.

Comparison of observed and expected probabilities of CBDS occurrence for the group II

Table 2

Patients	Predictor	observed % of CBDS	expected % of CBDS
entire group	previous cholecystectomy	66.7	81.8
entire group	bile duct dilation	78.9	66.7
without acute cholecystitis with bile duct dilation	Bi > 1.5N	71.4	81.8
age ≤ 70 years with bile duct dilation	3N < ALT < 7N or 12N < ALT	100	81.3

4. Discussion

Bilirubin and ALT were tested for every patient before ERCP. Bilirubin level was influenced by the presence of acute cholecystitis and by the presence of acute cholangitis, while patients with acute cholangitis also had acute cholecystitis. Even without detectable common bile duct obstruction, acute cholecystitis often causes mild elevations in the serum bilirubin concentrations. The elevated bilirubin level may be a consequence of haemathogenous or direct spread infection, which may cause structural and functional abnormalities of the liver. Since the patients with acute cholecystitis had elevated bilirubin levels even when CBDS was not present, the relationship between bilirubin level and CBDS was significant in patients with bile duct dilations after eliminations of patients with acute cholecystitis only.

References

[1] PRAT, F., MEDURI, B., DUCOT, B. et al.: Prediction of Common Bile Duct Stones by Noninvasive Tests. *Annals of surgery*, 229, 1999, 3, pp. 362–8.

We found the age to be a factor influencing ALT activity in patients with CBDS and bile duct dilation. Younger patients had higher ALT activity, older patients had elevated ALT activity but of a lesser degree than the younger ones. Two intervals of ALT values, as predictors of CBDS, are probably the result of age-dependent ALT activity as well as of possible spontaneous movement of the stones.

5. Conclusion

ERCP is indicated at patients with suspicion of ABP if biliary obstruction is present and if the presence of ductal stone is suspected. ERCP should have been used selectively because it is difficult, bothersome, expansive and has the potential of causing further pancreatic damage.

By using predictors we had established it is now possible to categorize patients according to the likelihood of CBDS occurrence. Providing predictive factors of biliary obstruction are not present it is useful to perform a less invasive or non-invasive investigation of bile ducts (EUS, MRCP), and ERCP and subsequent sphincterotomy should be indicated only if the presence of CBDS is confirmed by these methods.

Our results manifest that the definite predictive factor for CBDS is previous cholecystectomy and the bile duct dilation. Supporting predictors of these laboratory parameters, which were tested for every patient before ERCP, by patients with dilated bile ducts, influencing the probability of CBDS occurrence are the value of ALT in patients ≤70 years old and the level of Bi by patients without acute cholecystitis and cholangitis.

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- [2] ORIA, A., CIMMINO, D., OCAMPO, C. et al.: Early Endoscopic Intervention Versus Early Conservative Management in Patients with Acute Gallstone Pancreatitis and Biliopancreatic Obstruction: A randomized clinical trial, *Ann Surg* 245, 2007, (1), pp. 10-17.
- [3] NORTON, I.D., PETERSEN, B.T.: Acute and Chronic Pancreatitis Interventional Treatment of Acute and Chronic Pancreatitis, Endoscopic procedures. *Surg Clin North Am*, 79, 1999, 4, pp. 896-911.
- [4] MARK, D.H., LEFEVRE, F., FLAMM, C.R. et al: Evidence-based Assessment of ERCP in the Treatment of Pancreatitis. *Gastrointest Endosc*, Supplement to: 56, 2002, 6, pp. 249-54.
- [5] AGRETI, A., LOGIT, O.: Confidence Intervals for the Odds Ratio with Small Samples. *Biometrics* 55, 1999, pp. 597-602.
- [6] HORAKOVA, M., VADOVICOVA, I., KATUSCAK, I., JANIK, J., MAKOVNIK, P., SADLONOVA, J.: Consideration of Endoscopic Retrograde Cholangiopancreatography in Cases of Acute Biliary, *Pancreatitis*. *Bratislava Medical Journal*. Vol. 10, No. 9, 2009, pp. 553-558.