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ORIGINAL RESEARCH

Association between juxtapapillary diverticulum and acute cholangitis determined using laboratory data

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Abstract: The aim of this study was to evaluate the association between juxtapapillary diverticulum (JD) and acute cholangitis (AC), and to analyze laboratory data to reveal the underlying mechanism. We conducted a retrospective review of 139 patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) between April 2008 and March 2013 for diagnosis or treatment of biliary tract conditions. The Wilcoxon signed-rank test was used for comparison of variables between patients with or without JD. The χ^2 test was used to analyze the association between JD and AC duct dilatation. Logistic regression analysis was performed to identify variables with strong correlation with AC. ERCP was attempted in 139 patients, but in one patient the endoscope did not reach the papilla of Vater because of a partial gastrectomy, and in two patients evaluation for JD was not possible because of duodenal or papilla of Vater cancer. Therefore, 136 patients were included in this study. JD was significantly associated with AC ($P<0.0001$) and bile-duct dilatation ($P=0.0107$), and AC was strongly associated with bile duct dilatation ($P=0.0013$). Alkaline phosphatase levels were significantly elevated in patients with JD ($P=0.0237$). In AC patients without JD, χ^2 for C-reactive protein was 4.48 ($P=0.0342$), whereas in AC patients with JD, χ^2 values for the white blood cell count, alkaline phosphatase, and aspartate aminotransferase were 2.62, 3.1, and 3.61, respectively ($P=0.025$, 0.015, and 0.0336, respectively). JD was strongly associated with AC. Logistic regression analysis suggested that bile flow was disturbed with JD.

Keywords: logistic regression analysis, bile-duct dilatation, alkaline phosphatase, bile flow, papilla of Vater, Wilcoxon singed-rank test, χ^2 test

Introduction

Acute cholangitis (AC) is a bacterial infection caused by obstruction of the bile duct,[1–3] and should be treated promptly to prevent fatal sepsis.[4,5] Biliary drainage is usually performed through endoscopic retrograde cholangiopancreatography (ERCP),[6] but papillotomy is necessary for biliary drainage in the treatment of AC.[7] Juxtapapillary diverticulum (JD) is associated with an increased risk of cholangiopancreatic diseases, such as obstructive jaundice, AC, and acute pancreatitis.[8–10] The success rate of cannulation is controversial with ERCP for patients with JD,[11,12] the latter being a risk factor for sphincterotomy.[8] JD is an outpouching of mucosa and muscularis mucosa that arises in the duodenal window, located at the interruption of the duodenal muscle fibers where the common bile duct (CBD) and main pancreatic duct penetrate the duodenal wall.[13] The mechanism underlying the association between AC and JD, however, is not known. The aim of the present study was to compare laboratory variables in AC patients with or without JD to identify the potential mechanism underlying the association between these two conditions.

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Materials and methods

Patients

Patient records were retrospectively analyzed from April 2008 to March 2013. The institutional ethics committee reviewed our study, and determined that it was not a clinical trial because it was performed as a part of daily clinical practice. Written informed consent was obtained for each session of ERCP and from patients who underwent contrast-enhanced computed tomography (CECT) or magnetic resonance CP (MRCP). Patient anonymity was preserved. ERCP was performed for patients with suspected AC, bile-duct cancer, gallbladder cancer, pancreatic cancer, or intraductal papillary neoplasm. ERCP was also performed for patients with bile-duct stricture and other biliary or pancreatic conditions.[14] In this study, JD was not categorized.[12] Bile-duct dilatation was defined as a bile-duct diameter >7 mm as seen on abdominal ultrasonography, MRCP, CECT, or ERCP. The laboratory data analyzed in this study were white blood cell (WBC) count and C-reactive protein (CRP), total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase, and γ-glutamyl transpeptidase (γ-GTP) levels, all important variables for the diagnosis of AC.[6,15]

Diagnostic criteria for acute cholangitis

Patients were diagnosed with AC when they had fever, abdominal pain, and jaundice (Charcot's triad). If a patient did not meet the Charcot's triad criteria, AC was diagnosed when they showed an inflammatory response, consisting of fever and elevation of WBC count or CRP level, and biliary obstruction involving bile-duct dilatation, biliary stricture, CBD stones, and elevation of ALP or γ-GTP levels. The severity of AC was assessed following the Tokyo Guidelines.[16]

Table 1 Comparison of laboratory data between patients with and without juxtapapillary diverticulum

	Without juxtapapillary diverticulum (n=98)		With juxtapapillary diverticulum (n=37)		*P*-value
	Mean	95% CI	Mean	95% CI	
Age, years	69.2	67.2–71.2	69.0	65.7–72.3	0.8989
WBC	7,391	6,551–8,232	8,308	6,940–9,676	0.2610
CRP	2.62	1.57–3.67	4.12	2.39–5.85	0.1448
T-Bil	1.54	1.04–2.05	1.81	0.99–2.63	0.5821
ALP	447	365–529	626	495–757	0.0237
AST	119	77–160	124	57–192	0.8873
ALT	118	84–151	140	85–194	0.4962
γ-GTP	249	181–316	341	231–451	0.1575

Note: *P*-values were determined by Wilcoxon's signed-rank test.
Abbreviations: CI, confidence interval; WBC, white blood cell; CRP, C-reactive protein; T-Bil, total bilirubin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GTP, glutamyl transpeptidase.

Table 2 Comparison of laboratory data between patients with acute cholangitis with and without juxtapapillary diverticulum

	Without juxtapapillary diverticulum (n=27)		With juxtapapillary diverticulum (n=26)		*P*-value
	Mean	95% CI	Mean	95% CI	
Age	69.4	65.6–73.3	68.8	64.8–72.3	0.5989
WBC	10,122	8,075–12,169	9,080	6,995–11,166	0.3502
CRP	6.19	3.65–8.73	4.83	2.19–7.47	0.6207
T-Bil	2.93	1.59–4.27	2.03	0.67–3.40	0.8033
ALP	639	475–804	713	548–877	0.9854
AST	209	123–295	123	36–211	0.2332
ALT	204	131–276	149	78–220	0.5783
γ-GTP	350	227–474	382	256–508	0.5591

Note: *P*-values were determined by Wilcoxon's signed-rank test.
Abbreviations: CI, confidence interval; WBC, white blood cell; CRP, C-reactive protein; T-Bil, total bilirubin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GTP, glutamyl transpeptidase.

Endoscopic retrograde cholangiopancreatography

ERCP was performed by experienced endoscopists with a duodenoscope (JF-260V; Olympus, Tokyo, Japan). Papillotomy was performed with a pull-type sphincterotome (Boston Scientific, Natick, MA, USA). Stones and sludge were removed with a basket or balloon catheter, and a naso-biliary catheter was inserted for drainage if necessary.

Imaging diagnostics

Patients with suspected AC underwent CECT and abdominal ultrasonography to further investigate biliary dilatation, CBD stones, and cancer. After May 2012, the patients underwent MRCP with a 1.5 T scanner (Achieva Software version 3.2.2; Philips Medical Systems, Best, Netherlands). Before May 2012, some of the patients were referred to Sannou Hospital (Chiba City, Japan) for MRCP. CECT was performed using

Table 3 Correlation between juxtapapillary diverticulum and acute cholangitis or bile-duct dilatation

	Acute cholangitis (*P*<0.0001)		Bile-duct dilatation (*P*=0.0107)		Total
	–	+	–	+	
Juxtapapillary diverticulum					
–	72	27	59	40	99
+	11	26	13	24	37
Total	83	53	72	64	136

Note: *P*-values were determined by χ^2 test.

Table 4 Correlation between acute cholangitis and bile-duct dilatation

	Bile-duct dilatation		Total
	–	+	
Acute cholangitis			
–	53	30	83
+	19	34	53
Total	72	64	136

Note: P=0.0013 (χ^2 test).

a 16-detector-row CT scanner (Somatom Emotion 16; Siemens, Munich, Germany). Patients were administered intravenous contrast medium containing 100 mL of iopamidol at 3 mL/s (Konica Minolta Healthcare, Tokyo, Japan). CT images were acquired before the injection of contrast medium and at 30, 70, and 180 seconds later. Abdominal ultrasonography was performed by senior fellows at the Japan Society of Ultrasonics in Medicine with an SSA-700A instrument (Toshiba Medical Systems, Ohtawara, Japan) using a 5.0 MHz curved-array transcutaneous probe or an 8.0 MHz linear array transcutaneous probe.

Statistical analysis

The Wilcoxon signed-rank test was used for comparison of baseline variables. The χ^2 test was used to assess the association between JD and AC symptoms. Logistic regression analysis was performed to identify the variables that strongly correlated with AC. JMP software version 10.0.2 (SAS Institute, Cary, NC) was used for statistical analysis. $P<0.05$ was considered statistically significant.

Results

ERCP was attempted in 139 patients, but in one patient the endoscope did not reach the papilla of Vater because of a partial gastrectomy, and in two patients evaluation for JD was not possible because of duodenal or papilla of Vater cancer. Therefore, 136 patients were analyzed in this study.

The baseline characteristics of patients are shown in Table 1. Thirty-seven patients had JD (27.2%). Age was not correlated with the presence or absence of JD, but ALP level was significantly elevated in patients with JD (P=0.0237). No significant differences in baseline characteristics were noted between AC patients with JD or those without JD (Table 2).

Our analysis of the association of JD with AC or bile-duct dilatation (Table 3) revealed that JD was significantly associated with both AC ($P<0.0001$) and bile-duct dilatation (P=0.0107). The correlation of AC and bile-duct dilation was then analyzed with the χ^2 test (Table 4), which revealed a strong association of AC with bile-duct dilatation (P=0.0013).

Because symptoms are diagnostic clues to AC, we analyzed the correlation between JD and AC symptoms (Table 5). Although there was a tendency for a correlation of abdominal pain with JD, it was not significant (P=0.2117).

To reveal whether any laboratory data variables correlated with AC, logistic regression analysis was applied. The patients with AC were divided into those with or without JD. Table 6 shows the results of logistic regression analysis with AC patients without JD. The χ^2 of CRP was 4.48 (P=0.0342). For AC patients with JD, the χ^2 values for WBC count, ALP, and AST were 2.62, 3.1, and 3.16, respectively (P=0.0251, 0.015, and 0.0336, respectively; Table 7). No other laboratory parameters correlated with AC patients without JD.

Discussion

JD has been found in 32.8% of consecutive patients subjected to ERCP, and is classified into three types based on the position of the papilla of Vater: type 1, inside the diverticulum; type 2, in the margin of the JD; and type 3, near the JD.[12] In our series, JD was found in 27.2% of patients who underwent ERCP, which is consistent with previous reports.

It is reported that JD is associated with CBD stones and bile-duct dilatation,[8,17] although JD may be associated with bile-duct dilatation even in patients with normal levels of liver enzymes.[18,19] Our data are consistent with previous reports. It is speculated that the anatomical abnormalities of JD may play an important role in the formation of bile-duct pigment stones.[20]

Table 5 Correlation between juxtapapillary diverticulum and symptoms of acute cholangitis

	Abdominal pain (P=0.2117)		Total	Fever (P=0.6854)		Total	Jaundice (P=0.8928)		Total
	–	+		–	+		–	+	
Juxtapapillary diverticulum									
–	8	19		12	15		14	13	27
+	4	22		13	13		13	13	26
Total	24	45		25	28		27	26	69

Note: P-values were determined by χ^2 test.

Table 6 Logistic regression analysis of patients with acute cholangitis without juxtapapillary diverticulum

	χ^2	OR	95% CI of OR	*P*-value
WBC	1.61	1.0001084	0.999709–1.000055	0.2052
CRP	4.48	1.176696	0.721717–0.979098	0.0342
T-Bil	1.49	1.1781629	0.580052–1.057499	0.2226
ALP	1.1×10^{-6}	0.9999953	0.997434–1.002703	0.9972
AST	0.19	1.001254	0.991369–1.004106	0.6660
ALT	0.27	1.0018022	0.991558–1.00594	0.6040
γ-GTP	0.03	1.0002375	0.991558–1.002736	0.8616

Note: *P*-values were determined by logistic regression analysis.
Abbreviations: OR, odds ratio; CI, confidence interval; WBC, white blood cell; CRP, C-reactive protein; T-Bil, total bilirubin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GTP, glutamyl transpeptidase.

The relation between bile-duct dilatation and AC is strong enough for bile-duct dilatation to be a criterion for the diagnosis of AC, possibly suggesting bile-duct obstruction.[16] On the other hand, the mechanism underlying the association between JD and bile-duct dilatation is unclear.

In the present study, ALP levels were higher in patients with JD than in those without JD. With regard to only patients with AC, there was no difference in ALP levels between patients with or without JD. These data suggest that bile flow might be disturbed with JD. Once AC occurs and ALP level is elevated, any difference between patients with and without JD may be obscured. The incidence of positive bacterial bile cultures is significantly higher in patients with JD than in those without,[21] which combined with our data suggests that bile flow might be disturbed with JD and that bacterial infection is present more often in the bile ducts of patients with JD than in those without. Therefore, bile-duct pigment stones formed more often in patients with JD than in those without.[20]

The sphincter of Oddi regulates bile flow and prevents AC.[22] AC is caused by obstruction of the bile duct, mainly by CBD stones.[1,2] In the present study, the laboratory variables correlating with AC were different between patients with or without JD. CRP was the only variable that correlated with AC in patients without JD, whereas WBC count and ALP and AST levels were correlated with AC in patients with JD. WBC count and CRP level indicate inflammation, whereas ALP and AST levels represent bile-duct obstruction. Our data suggest that bile flow was disturbed in patients with JD. It has been speculated that JD disturbs the motility of the duodenum and pressure of the sphincter of Oddi, leading to increased infection of the bile duct in concert with bacterial overgrowth in the diverticulum. The infection might be enhanced in the presence of edema and partial obstruction of the bile duct with CBD stones. This hypothesis could be demonstrated by measuring bile-duct pressure with a manometer during ERCP.[23] A potential concern is that JD could be a risk factor for complications, such as bleeding, infection, and acute pancreatitis. To reduce this risk, endoscopic papillary large-balloon dilatation is recommended for patients with JD.[24] It would be preferable for AC patients with JD to undergo more frequent follow-ups after treatment, because they could be prone to AC relapse. Further studies measuring the pressure of the sphincter of Oddi using a manometer are needed to provide more details of this association. In conclusion, our study findings showed that JD was strongly associated with AC and that bile flow was disturbed with JD, based on laboratory data.

Table 7 Logistic regression analysis of patient with acute cholangitis with diverticulum

	χ^2	OR	95% CI of OR	*P*-value
WBC	2.62	1.000497	0.998739–0.999954	0.0251
CRP	2.98	0.6993023	0.987904–2.373463	0.0582
T-Bil	1.17	1.77331172	0.168276–1.456388	0.2509
ALP	3.10	1.0044708	0.988934–0.999331	0.0150
AST	3.61	0.989096	1.000797–1.024472	0.0336
ALT	0.28	1.0033479	0.982806–1.008615	0.5874
γ-GTP	0.08	1.0005787	0.994856–1.003876	0.7741

Note: *P*-values were determined by logistic regression analysis.
Abbreviations: OR, odds ratio; CI, confidence interval; WBC, white blood cell; CRP, C-reactive protein; T-Bil, total bilirubin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GTP, glutamyl transpeptidase.

Disclosure

The authors report no conflicts of interest in this work.

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