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BRIEF ARTICLES

Acute transient hepatocellular injury in cholelithiasis and cholecystitis without evidence of choledocholithiasis

Chen-Wang Chang, Wen-Hsiung Chang, Ching-Chung Lin, Cheng-Hsin Chu, Tsang-En Wang, Shou-Chuan Shih

Chen-Wang Chang, Wen-Hsiung Chang, Ching-Chung Lin, Cheng-Hsin Chu, Tsang-En Wang, Division of Gastroenterology, Department of Internal Medicine, Mackay Memorial Hospital, Mackay Medicine, Nursing and Management College, Taipei 10449, Taiwan, China
Shou-Chuan Shih, Division of Gastroenterology, Department of Internal Medicine, Health Evaluation Center, Mackay Memorial Hospital, Mackay Medicine, Nursing and Management College, Taipei 10449, Taiwan, China
Author contributions: Chang CW and Shih SC contributed to the study design, data collection and manuscript correction and editing; Chang WH, Lin CC and Wang TE analyzed and interpreted the data; Chu CH approved the final version of the paper.
Correspondence to: Shou-Chuan Shih, MD, Division of Gastroenterology, Department of Internal Medicine, Mackay Memorial Hospital, No. 92, Sec. 2, Chung-Shan N. Road, Taipei 10449, Taiwan, China. mmhgiman@gmail.com
Telephone: +886-2-25433535 Fax: +886-2-25433642
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Abstract

AIM: To investigate acute transient hepatocellular injury in patients with cholelithiasis and cholecystitis but no evidence of choledocholithiasis.

METHODS: The medical records of patients with cholelithiasis who underwent cholecystectomy between July 2003 and June 2007 were retrospectively reviewed. Imaging studies to detect common bile duct (CBD) stones were performed in 186 patients, who constituted the study population. Biochemical liver tests before and after surgery, and with the presence or absence of CBD stones were analyzed.

RESULTS: In 96 patients with cholelithiasis and cholecystitis without evidence of CBD stones, 49 (51.0%) had an alanine aminotransferase level elevated to 2-3 times the upper limit of normal, and 40 (41.2%) had an elevated aspartate aminotransferase level. Similar manifestations of hepatocellular injury were, as would be expected, even more obvious in the 90 patients with CBD stones. These markers of hepatocellular injury resolved almost completely within 2 wk to 1 mo after cholecystectomy. Compared to 59 patients with histologically less severe cholecystitis in the group undergoing urgent surgery (total 74 patients), the 15 patients with a gangrenous gallbladder had a higher mean level of total bilirubin (1.14 ± 1.27 mg/dL *vs* 2.66 ± 1.97 mg/dL, $P < 0.001$) and white cell count (9480 ± 4681/μL *vs* 12840 ± 5273/μL, $P = 0.018$).

CONCLUSION: Acute hepatocellular injury in cholelithiasis and cholecystitis without choledocholithiasis is mild and transient. Hyperbilirubinemia and leukocytosis may predict severe inflammatory changes in the gallbladder.

Key words: Acute transient hepatitis; Cholelithiasis; Cholecystitis; Hyperbilirubinemia; Leukocytosis

Peer reviewer: Emmet B Keeffe, MD, Professor, Chief of Hepatology, Medical Director, Liver Transplant Program, Program Director, Gastroenterology Fellowship, Stanford University Medical Center, 750 Welch Road, Suite 210, Palo Alto, CA 94304, United States

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INTRODUCTION

Although viral hepatitis is quite prevalent in Taiwan, viral infection is by no means the only cause of acute hepatitis[1]. One setting in which there may be acute inflammation of the liver parenchyma is the presence of common bile duct (CBD) stones and cholangitis, situations in which liver tests have been widely studied[2-4]. We have found few investigations, however, of biochemical evidence of hepatocellular injury (hepatitis) in patients with cholelithiasis and cholecystitis who do not have CBD stones.

Hepatocellular injury is indicated by increases in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The severity of such injury may be reflected in decreased hepatic production of

certain products such as albumin and clotting factors. Inflammation or damage to the biliary tract is signaled by an increase in alkaline phosphatase (ALK-P), which is sometimes confirmed by measuring gamma-glutamyltransferase. Serum bilirubin levels may be elevated in both biliary tract and hepatocellular diseases. Discussion of this topic is therefore often confusing when the general term is used rather than the names of particular biochemical markers of interest.

We designed this study to address the specific question of how often hepatocellular injury occurs in patients with cholelithiasis and cholecystitis in the absence of CBD stones, as opposed to cases where CBD stones/obstruction were found. We also wanted to see if there was any correlation between the degree of hepatocellular injury and the severity of the cholecystitis.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of patients admitted to Mackay Memorial Hospital, Taipei, from July 2003 to June 2007 who underwent cholecystectomy for cholelithiasis associated with cholecystitis (acute or chronic). Of 1168 such records, we retrieved those of patients who had undergone either preoperative endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) or intra-operative cholangiography. The imaging procedures were done to determine whether CBD stones were present in patients who had either sonographic evidence of a dilated CBD and/or biochemical evidence suggesting biliary tract obstruction. The cholecystectomized patients who had biochemical or sonographic evidence suspicion of a CBD disorder but refused to undergo invasive imaging such as ERCP, were not included in the study. Patients with viral hepatitis (that is, hepatitis A, hepatitis B or C virus infection), alcoholic liver disease, drug-related hepatitis, metabolic liver disease, autoimmune hepatitis, pancreatitis, or a previous history of ERCP with endoscopic sphincterotomy for removal of CBD stones were excluded. The liver tests analyzed for this study included AST, ALT, ALK-P, and total and direct bilirubin. The peripheral leukocyte count was also recorded. All the patients had stones in the gallbladder as demonstrated by sonography, and also in the operative specimens. Cholecystitis was diagnosed and its severity graded on the basis of the pathology examination as either gangrenous or simple cholecystitis.

Statistical analysis

The Student *t*-test was used to analyze differences between groups. We compared the liver tests (including AST, ALT, ALK-P, direct bilirubin and total bilirubin) in patients with cholelithiasis or cholecystitis who underwent cholecystectomy with or without CBD stones. We also compared the liver tests in patients with a histological diagnosis of gangrenous *vs* simple cholecystitis, but only in those without evidence of CBD stones. $P < 0.05$ was considered significant.

RESULTS

Of all 1168 records, 186 patients (92 males, 94 females) met the study inclusion criteria. The number of patients with cholelithiasis and abnormal liver function tests was more than 186. However, as the aim of our study was to ensure the status of the CBD, we only included patients whose CBDs were evaluated using imaging procedures. In the included 186 patients, a total of 226 imaging procedures for evaluation of CBD were performed, with 114 instances of ERCP, three of MRCP, and 109 of intra-operative cholangiography. CBD stones were found in 90 patients. It was very remarkable that few MRCPs were done in comparison to ERCPs and intra-operative cholangiographies. It was because of a limitation of the medical insurance system in Taiwan. Cholecystectomy was performed urgently in 154 patients and electively in 32 (Table 1). The method of cholecystectomy was laparoscopic in 142 and conventional in 44. In patients who underwent an urgent procedure, acute right upper quadrant or epigastric pain had been present for no more than 2 d prior to surgery. Those undergoing elective surgery had had at least one recent episode of pain typical of biliary tract disease and had been deemed to have symptomatic cholelithiasis.

Most of the liver tests were abnormal, not only in patients with stones both in the gallbladder and the CBD, but also in patients with stones limited to the gallbladder. However, the mean values in patients with CBD stones were significantly higher than those in patients without evidence of CBD stones. Of the 96 patients without evidence CBD stones, 49 (51.04%) had an elevated ALT, averaging 2-3 times the upper limit of normal. A slightly lower proportion (41.67%) also had an elevated AST. The highest AST was 670 IU/dL and the highest was ALT 566 IU/dL. Mild elevations of serum total bilirubin and ALK-P were also present in 27% and 23%, respectively, of these patients (Table 2). Among these 96 patients, 82 patients were seen for follow-up 2 wk to 1 mo after cholecystectomy, by which time the mean values of the liver tests had almost returned to normal, with only the mean ALT still slightly elevated, but already much lower than the preoperative level (Table 3).

There were 74 patients who had cholelithiasis and cholecystitis without evidence of CBD stones and who underwent urgent cholecystectomy. The gallbladder histology revealed gangrenous cholecystitis in 15 patients. The only significant differences between that group and the 59 patients with simple cholecystitis were a higher bilirubin level (1.14 ± 1.27 mg/dL *vs* 2.66 ± 1.97 mg/dL, $P < 0.001$) and white cell count ($9480 \pm 4681/\mu L$ *vs* $12840 \pm 5273/\mu L$, $P = 0.018$). The aminotransferase and ALK-P levels did not differ significantly between the two groups (Table 4).

DISCUSSION

Hepatocellular injury in patients with cholecystitis is usually attributed to injury related to CBD stones. However,

Table 1 Basic data of 186 patients with cholelithiasis and cholecystitis who underwent cholecystectomy (mean ± SD)

Cholecystectomy	CBD stones	Patients (M/F)	Age (yr)	ERCP	MRCP	IOC
Urgent	Yes	80 (43/37)	63.8 ± 16.2	47	3	61
	No	74 (33/41)	57.9 ± 15.9	42	0	34
Elective	Yes	10 (7/3)	59.8 ± 11.1	9	0	6
	No	22 (9/13)	58.2 ± 15.4	16	0	8
	Total	186	60.6 ± 15.9	114	3	109

CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography; MRCP: Magnetic resonance cholangiopancreatography; IOC: Intra-operative cholangiography.

Table 2 Liver tests in patients with cholelithiasis and cholecystitis who underwent cholecystectomy

Variable (normal range)	CBD stones (90)		No CBD stones (96)		*P*-value[1]
	mean ± SD (range)	Incidence of abnormal results	mean ± SD (range)	Incidence of abnormal results	
AST (5-35 IU/L)	137.2 ± 131.8 (19-693)	84.40% (76/90)	62.9 ± 96.9 (10-670)	41.67% (40/96)	< 0.001
ALT (5-30 IU/L)	178.7 ± 159.0 (17-696)	95.55% (86/90)	83.8 ± 109.5 (12-566)	51.04% (49/96)	< 0.001
ALK-P (40-133 IU/L)	204.7 ± 122.7 (14-672)	71.11% (64/90)	118.8 ± 92.5 (38-615)	22.92% (22/96)	< 0.001
D. Bilirubin (0.0-0.4 mg/dL)	2.16 ± 2.08 (0.1-12)	88.89% (80/90)	0.64 ± 1.01 (0-5.0)	32.29% (31/96)	< 0.001
T. Bilirubin (0.2-1.3 mg/dL)	3.81 ± 3.27 (0.3-18.6)	76.67% (69/90)	1.50 ± 1.68 (0.2-9.3)	27.08% (26/96)	< 0.001

[1]Statistical analysis using the Student's *t*-test. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALK-P: Alkaline phosphatase; D.: Direct; T.: Total.

Table 3 Liver tests before and 2 wk to 1 mo after cholecystectomy in 82 patients without CBD stones (mean ± SD)

Value (normal range)	Before	After
AST (5-35 IU/L)	62.89 ± 96.85	30.95 ± 15.14
ALT (5-30 IU/L)	83.80 ± 109.50	35.95 ± 26.05
ALK-P (40-120 IU/L)	118.83 ± 92.53	118.79 ± 78.05
D. Bilirubin (0.0-0.4 mg/dL)	0.64 ± 1.00	0.37 ± 0.31
T. Bilirubin (0.2-1.3 mg/dL)	1.50 ± 1.68	0.90 ± 0.58

we have demonstrated that patients with cholecystitis and cholelithiasis but without evidence of CBD stones may also have elevated serum aminotransferase levels. Although the liver test abnormalities in such patients in our study were milder on average than in those with CBD stones, the highest ALT (566 IU/L) and total bilirubin (9.3 mg/dL) levels were still quite striking.

Pathologically, liver changes such as chronic cholestasis or portal-portal linking fibrosis are a common finding in patients with cholelithiasis with CBD stones. However, other non-specific changes in liver histology are also found in patients without CBD stones[5]. In our study, hepatocellular injury (diagnosed clinically by elevation of aminotransferases and bilirubin levels) was common regardless of whether or not CBD stones were present. The incidence was higher and the aminotransferase elevations were more marked in those with stones[6], but a substantial proportion of patients without CBD stones also had some degree of hepatocellular injury. In most patients, the AST, ALT, and bilirubin levels had almost returned to normal 2 wk to 1 mo after cholecystectomy (Table 3). This hepatocellular injury appeared to be a transient, reactive phenomenon secondary to cholecystitis associated with cholelithiasis, whether or not there had been stones in the CBD. This kind of hepatocellular injury, even showing relatively high serum levels of aminotransferases and bilirubin, should not be an obstacle to preparation of these patients for surgical intervention. Its activity is transient and mild. It needs no further management and will resolve spontaneously as expected, assuming the diseased gallbladder is removed.

There are two main origins of ALK-P: the liver and bone. An elevated serum ALK-P found to originate from the liver, particularly if it persists for a period of time, suggests prolonged cholestasis[7]. In our patients in whom no CBD stones were identified, the mean serum ALK-P was not significantly elevated (Table 2), implying that they had no obvious biliary obstruction before operation. In general, there are two distinct patterns of liver injury: one is hepatocellular damage demonstrated clinically by elevated levels of the aminotransferases but with a relatively normal ALK-P; the other is that of cholestasis with an ALK-P elevated out of proportion to the aminotransferases. It is not difficult to understand why hepatocellular damage, and hence elevations of the aminotransferase levels, would occur in the presence of CBD stones. Higher biliary tree pressures can lead to impaired bile secretion, retention of bile acids, and consequent apoptosis or necrosis of hepatocytes[7]. However, the exact mechanism of hepatocellular damage in cholecystitis associated with cholelithiasis but without choledocholithiasis is not fully understood. Presumably such patients have normal biliary pressure. Free radical reactions in the human gallbladder have been demonstrated to occur in cholecystitis, suggesting that oxidative stress may partially account for liver injury[8,9]. It may also be that inflammation in the gallbladder induces inflammation in the closely apposed neighboring liver tissue. However, elevation of aminotransferases could not be explained based on the proximity effect

Table 4 Comparison of basic data between gangrenous cholecystitis and simple cholecystitis in patients who underwent urgent surgery (total 74 patients) (mean ± SD)

Variable	Gangrenous cholecystitis (15)	Simple cholecystitis (59)	*P*-value	95% CI	
				Lower	Upper
Age	64.9 ± 11.8	56.1 ± 16.4	0.053	-17.83	0.13
Hospital stay (d)	13.3 ± 5.6	11.0 ± 8.7	0.334	-7.01	2.41
AST (5-35 IU/L)	61.5 ± 74.4	72.8 ± 116.3	0.721	-51.76	74.42
ALT (5-30 IU/L)	72.3 ± 66.8	110.8 ± 187.1	0.438	-59.78	136.74
ALK-P (40-120 IU/L)	128.1 ± 68.9	103.7 ± 48.5	0.116	-55	6.19
D. Bilirubin (0.0-0.4 mg/dL)	1.23 ± 1.31	0.41 ± 0.70	0.001	-1.31	-0.33
T. Bilirubin (0.2-1.3 mg/dL)	2.66 ± 1.97	1.14 ± 1.27	< 0.001	-2.35	-0.69
WBC (3400-10000/μL)	12840.0 ± 5273.9	9480.2 ± 4681.3	0.018	-6128	-591.6

alone since it bears no relation to prognosis of severe acute cholecystitis[10]. On the other hand, severity of acute cholecystitis also had no significant influence on the level of serum aminotransferases[11].

Jaundice is a common feature of patients with CBD stones[12]. In fact, it is not a rare manifestation of gallbladder disease without evidence of CBD stones; the difference is that in the latter, the serum total bilirubin level is usually less than 4 mg/dL[13,14]. In our patients without evidence of CBD stones, the mean total bilirubin level of 1.5 mg/dL was comparable with reports in the literature. However, the highest value of up to 9.3 mg/dL means that hyperbilirubinemia beyond the so-called 'mild degree' will not always suggest a complicated condition of gallstone disease.

Peng *et al*[11] documented that the severity of inflammation in cholecystitis with CBD stones did not influence the level of aminotransferases and bilirubin. However, the severity of inflammation was defined as acute attack or not. In our study, the definition of severity is based on the gallbladder histology (simple or gangrenous cholecystitis). In patients with gangrenous cholecystitis, while aminotransferase levels were not particularly elevated, the mean serum bilirubin was significantly higher than that in patients with simple cholecystitis (Table 4). Diabetes mellitus and leukocytosis have been associated in some studies with gangrenous cholecystitis, but hyperbilirubinemia has not[15-17]. However, these studies did not exclude patients with CBD stones, which may have skewed the comparison between those with and without a gangrenous gallbladder. For this comparison, we also analyzed only patients without evidence of CBD stones and found that leukocytosis as well as hyperbilirubinemia were associated with more severe, i.e. gangrenous, cholecystitis.

There could be the possibility that small stones passed through the duct during biliary colic so as to result in biochemical liver function abnormalities. Our results seemed not to favor this proposal. Firstly, ERCP (most of our patients underwent ERCP examination) is so far the most reliable (both sensitivity and specificity are over 95%) and widely applicable imaging procedure to evaluate the CBD, even in the elderly[18,19]. Our judgment of further management for the patients mainly depended on these evaluations. Secondly, small stones that pass through the duct, especially stones less then 0.5 cm in diameter, may induce pancreatitis[20]. We excluded patients with pancreatitis to reduce this possible confounding factor. Finally, the averaged normal ALK-P levels in the group without evidence of CBD stones also argues against transient stone passage as a cause of the hepatocellular injury.

The limitation of our study is that it was a retrospective observation. We selected patients who underwent image evaluation of the CBD because of suspicion of biliary obstruction from abnormalities in biochemical liver function and/or sonography. The elevated aminotransferase levels in the group of patients may have resulted in a falsely high incidence of hepatocellular injury induced by gallbladder disease without CBD stones. However, regardless of the pathophysiology and true occurrence rate, the abnormal biochemical liver function of almost all the patients resolved rapidly and spontaneously after cholecystectomy. This phenomenon implied that the transient hepatocellular injury was brought about by symptomatic gallstones with cholecystitis even in the absence of CBD stones.

We observed persistently high liver enzymes in one patient who was subsequently found to have cancer of the Ampulla of Vater. This suggests that if there is incomplete postoperative resolution of the abnormal tests, residual or additional pathology should be investigated. However, in the absence of other symptoms, it would be reasonable to wait for 1 mo to see if the hepatocellular injury resolves before initiating more invasive studies such as ERCP.

COMMENTS

Background

Acute hepatocellular injury is a commonly encountered phenomenon in patients with cholelithiasis and concomitant common bile duct (CBD) stones. However, in clinical practice, it seemed to occur also in cholelithiasis patients without evidence of CBD stones. Its incidence and final outcome necessitated clarification.

Research frontiers

Abnormal liver function tests for predicting CBD stones have been well discussed, however, the relationship between liver function and cholelithiasis/cholecystitis alone is not well understood.

Innovations and breakthroughs

In this study, the authors studied a phenomenon of hepatocellular injury in patients with cholelithiasis without evidence of concomitant stones in the CBD. It was transient and resolved spontaneously after cholecystectomy.

Applications

This kind of hepatocellular injury, even showing relatively high serum levels of aminotransferases and bilirubin, should not be an obstacle to preparation of such patients for surgical intervention. The abnormalities will be expected to recover spontaneously and need no further investigation or treatment unless they persist for more than 1 mo.

Peer review

This is an interesting paper addressing an acute transient hepatocellular injury which is often presented but ignored. The article is well balanced and the discussion is clear and exhaustive.

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