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Biliary tract disease and acute non–A-E hepatitis in Hong Kong: prospective study

在香港的膽管疾病和急性非甲至戊型肝炎：預期研究

Objective. To investigate the role of biliary tract disease in patients with acute non–A-E hepatitis.
Design. Prospective study.
Setting. Infectious diseases unit, government hospital, Hong Kong.
Patients. Sixty-one consecutive patients, admitted with the diagnosis of acute hepatitis and negative hepatitis serology for hepatitis A, B, C, D and E virus.
Main outcome measures. Abdominal ultrasound and endoscopic retrograde cholangiopancreatography findings; clinical outcome.
Results. Ultrasonographic abnormalities indicating biliary tract disease were found in 30% (18/61) of patients. Endoscopic retrograde cholangiopancreatography performed in 78% (14/18) of patients with abnormal ultrasound finding(s), confirmed the presence of biliary tract disease. Age, sex, serum alanine aminotransferase level, and serum albumin level were independent predictors of biliary tract disease in the patients studied.
Conclusion. Biliary tract diseases were found in 20% of patients with acute non–A-E hepatitis. Serum amylase and abdominal ultrasonography should be performed for all patients presenting with acute non–A-E hepatitis. Endoscopic retrograde cholangiopancreatography is indicated for those with apparent gallstones or abnormal biliary tract findings.

目的：研究患上急性非甲至戊型肝炎的患者中膽管疾病的角色。
設計：預期研究。
安排：香港政府醫院的傳染病科。
患者：連續61名被診斷為急性肝炎但對甲、乙、丙、丁、戊型肝炎病毒血清學呈陰性的患者。
主要結果測量：腹部超聲波和內窺鏡逆行性胰膽管造影術的發現；臨床結果。
結果：超聲描記術的不正常結果顯示30% (18/61)患者有膽管疾病，而78% (14/18)有反常超聲波發現的患者進行的內窺鏡逆行性胰膽管造影術亦證實了膽管疾病的存在。年齡、性別、血清丙氨酸轉氨酶水平、和血清白蛋白水平是所研究的患者中膽管疾病的獨立預報指標。
結論：在急性非甲至戊型肝炎患者中，有20%發現有膽管疾病。對所有急性非甲至戊型肝炎患者都應進行血清澱粉酶和腹部超聲描記術。而對那些有明顯膽石或膽管有異常發現的患者需要進行內窺鏡逆行性胰膽管造影術。

Key words:
Biliary tract;
Endoscopic retrograde cholangiopancreatography;
Hepatitis;
Ultrasonography

關鍵詞：
膽管；
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Introduction

Despite the discovery of the hepatitis E virus, it is apparent that 3% to 20% of cases of acute hepatitis, are still negative for all known viral markers.[1-4]

Recently, two further viruses—hepatitis G virus and transfusion-transmitted virus—have been detected and successfully cloned.[5,6] These viruses account for a minority of acute non–A,B,C,D,E (non–A-E) hepatitis cases, however.[4,7,8] Furthermore, their pathogenic role remains open to question.[9] It has also been reported that non–A-E hepatitis is associated with the presence of autoantibodies. This does not in itself imply an autoimmune causation since a significant proportion of patients with acute hepatitis A or B also show the transient presence of autoantibodies.[10,11]

Biliary tract disease has to be excluded in patients with acute non–A-E hepatitis. Common bile duct stones can be asymptomatic. On the other hand, bile duct obstruction, complicated by acute bacterial cholangitis and acute biliary pancreatitis constitute serious complications, associated with high mortality rates. Suggestive clinical features, namely fever, chills, and abdominal pain, may be absent in up to 70% of patients with cholangitis confirmed by operative findings.[12] Marked elevation of serum alanine aminotransferase (ALT) has been reported in patients with acute cholecystitis, choledocholithiasis, and gallstone pancreatitis.[13-15] Most reports, however, have not excluded biliary tract disease as a cause of elevated serum ALT levels in non–A-E hepatitis,[1,2,4] whereas a further study did not outline the means of exclusion utilised.[3] Patients with acute cholangitis and gallstone pancreatitis can be managed effectively by urgent endoscopic drainage,[16] together with the use of appropriate antibiotics.[17]

The aims of this study were to investigate the role of biliary tract disease in patients with acute non–A-E hepatitis, and to identify any predictive factors for biliary tract diseases in this patient group.

Methods

Selection of patients

This study was conducted prospectively between January 1996 and December 1997. A total of 724 patients aged 15 years or older, with a diagnosis of acute hepatitis, were admitted to the Infectious Disease Unit at the Princess Margaret Hospital, a referral centre for patients with acute viral hepatitis, during the study period. Patients with a presumptive diagnosis of acute non–A-E hepatitis were enrolled in the study. The diagnosis of acute viral hepatitis was based on a suggestive history, typical symptoms and signs of acute hepatitis, and an increase in the serum ALT level in excess of ten times the normal upper limit (>400 U/L). Patients with a history and/or clinical features suggestive of acute cholangitis—fever, with a temperature higher than 38.5°C, chills, severe abdominal pain and tenderness, and a marked increase in serum alkaline phosphatase level—were excluded, as were patients with a history consistent with drug-induced liver disease and alcohol misuse, serological evidence of autoimmune hepatitis, or metabolic causes of hepatitis. Patients with mild epigastric pain, or right upper quadrant abdominal pain not suggestive of biliary colic were included.

Diagnoses of acute hepatitis A, B, C, D and E were made according to the seropositivity of hepatitis A virus immunoglobulin M (IgM) on enzyme-linked immunosorbent assay (Vidas, bio-Merieux Vitek Inc., Lyon, France), anti-hepatitis B core (HBc) IgM and hepatitis B surface antigen (HBsAg) by enzyme immunoassays (Abbott Laboratories, Chicago, Illinois, USA), anti-hepatitis C virus (HCV) by second generation enzyme immunoassay (Ortho Diagnostic Systems, Ravitan, New Jersey, USA), anti-hepatitis D virus by enzyme immunoassay (Abbott Laboratories, Chicago, Illinois, USA) and anti-hepatitis E virus IgM by enzyme immunoassay (DBL/Genelabs Technologies Inc., Genelabs, Singapore), respectively. Patients with positive HBsAg and negative anti-HBc IgM results were diagnosed with an exacerbation of chronic hepatitis B and hence were excluded. Patients with negative anti-HCV on admission were rechecked 6 months later. The diagnosis of acute non–A-E hepatitis was established when all of the above tests were negative. Patients with a diagnosis of acute non–A-E hepatitis were categorised into two subgroups: non–A-E hepatitis with biliary tract disease and non–A-E hepatitis without biliary tract disease. The presence of an isolated gallbladder stone without evidence of acute cholecystitis or ductal abnormalities on endoscopic retrograde cholangiopancreatography (ERCP), was not defined as biliary tract disease in this study.

Routine investigations for non–A-E hepatitis

All patients with acute non–A-E hepatitis underwent abdominal ultrasonography. Liver biopsy was offered, if liver function test results remained deranged for over 6 months. Blood tests, including antinuclear factor, anti–double-stranded DNA, anti-smooth muscle and anti-mitochondrial antibodies, immunoglobulin pattern, serum copper and ceruloplasmin, and iron status, were completed to exclude other causes of liver impairment. Serum amylase was monitored and ERCP offered, if ultrasound findings revealed a gallstone and/or a dilated biliary tract. A common bile duct diameter greater than 7 mm on ultrasound measurement was defined as a dilated common bile duct, irrespective of

the presence of an intact gallbladder.[18] A diagnosis of acute pancreatitis was made if the serum amylase level was higher than 1000 IU/L. Endoscopic retrograde cholangiopancreatography films of all patients were reviewed separately by two endoscopists, blinded to the ultrasound findings, and a consensual diagnosis reached. On ERCP, common bile duct diameter measurements of less than 6 mm, between 6 to 10 mm, and greater than 10 mm, were defined as normal, borderline-sized, and dilated, respectively.[19-21] Papillotomy was performed for patients with a borderline-sized or dilated common bile duct on ERCP. If a ductal stone was found, basket or balloon extraction was performed, with or without prior mechanical lithotripsy. This was followed by occlusive cholangiography, to confirm complete stone extraction.

Statistical analysis

All numerical results were expressed as a median and range. Dichotomous variables were compared using the Chi squared test or the two-tailed Fisher's Exact test. Continuous variables were compared by the Mann Whitney U test. The statistical significance level was $P<0.05$. To identify predictive factors for biliary tract diseases in patients with acute non–A-E hepatitis, multivariate analysis using logistic regression by forward stepwise method was applied to the following factors: age, sex, white cell count, platelet count, prothrombin time, serum albumin level, serum globulin level, bilirubin level, serum alkaline phosphatase, and ALT level. At each step, a variable was entered into the model if the probability of its score statistic was less than 0.05. A variable was removed if its score statistic had a probability greater than or equal to 0.10.

Table 1. Number of patients with various types of acute hepatitis

Type of hepatitis	Number of patients, n=697 No. (%)
A	362 (51.9)
B	229 (32.9)
C	3 (0.4)
D	1 (0.1)
E	41 (5.9)
Non–A-E	61 (8.8)

Results

Of a total 724 patients admitted with acute hepatitis, 27 patients with various non-viral causes of liver impairment—10 with clinical cholangitis, 3 with autoimmune hepatitis, 3 with drug-induced hepatitis, 10 with alcoholic hepatitis, and 1 with Wilson's disease— were excluded. Sixty-one (8.8%) of the remaining patients were diagnosed with acute non–A-E hepatitis (Table 1). Patients with non–A-E hepatitis were significantly older than patients with A to E hepatitis. Although blood counts and liver enzyme levels showed overlap between the two groups, patients with non–A-E hepatitis had significantly higher white cell counts and lower ALT levels than patients with acute A to E hepatitis (Table 2).

Biliary tract disease in patients with non–A-E hepatitis

Ultrasonographic abnormalities were found in 29.5% (18/61) of patients with non–A-E hepatitis. Thirteen patients had isolated gallstones, with no dilation of the biliary tract. A dilated biliary tract, without a gallstone, was detected in four patients. The presence of a gallstone, associated with a dilated biliary tree, was found in only one patient. A thickened gallbladder wall, suggestive of acute cholecystitis was not seen in any of the patients with non–A-E hepatitis.

Table 2. Comparison of demographic data and laboratory results for patients with hepatitis A to E and non–A-E hepatitis

	Hepatitis A to E, n=636	Non–A-E hepatitis, n=61	P value
Demographic data			
Sex (M/F)*	465/171	40/21	0.208
Age† (years)	28 (15-77)	35 (16-73)	<0.001
Haematological results†			
Haemoglobin (g/L)	139 (62-198)	143 (96-193)	0.275
White cell count (x 10^9 /L)	6.2 (2.4-14.7)	6.7 (2.9-17.4)	<0.001
Platelet count (x 10^9 /L)	198 (59-450)	224 (64-440)	0.126
Prothrombin time (seconds)	11 (10-27)	11 (10-32)	0.275
Liver function tests†			
Serum albumin (g/L)	40 (24-49)	40 (31-49)	0.590
Serum globulin (g/L)	33 (14-58)	33 (21-55)	0.879
Bilirubin (mmol/L)	100 (7-1087)	117 (8-637)	0.416
Alkaline phosphatase (U/L)	197 (24-740)	191 (65-573)	0.606
Alanine aminotransferase (U/L)	2210 (412-8120)	1190 (400-6496)	<0.001
Serum amylase (U/L)	87 (29-395)	98 (14-3408)	0.672

* Comparison by the Chi squared test. All other comparisons were made by Mann-Whitney U test
† Results are expressed as median (range)

Table 3. Endoscopic retrograde cholangiopancreatography findings and final diagnosis for 14 patients with acute non–A-E hepatitis and abnormal ultrasonographic findings

Final diagnosis	Ultrasonographic findings			Endoscopic retrograde cholangiopancreatography		
	Normal duct	Dilated duct	Gall-stone	Normal duct	Dilated duct	Ductal stone
Cholangitis (n=2)	1	1	2	0	2 (1 borderline-sized)	2
Pancreatitis (n=3)	1	2	1	0	3 (2 borderline-sized)	1
Bile ductal stone(s) (n=6)	4	2	5	2	4 (1 borderline-sized)	5 (1 sludge)
Dilated biliary tract only (n=1)	0	1	0	0	1	0
Isolated gallstone (n=2)	2	0	2	2	0	0
Total (n=14)	8	6	10	4	10 (4 borderline-sized)	9 (1 sludge)

Fourteen of the 18 patients with abnormal ultrasound findings, agreed to an ERCP examination. Three of the remaining patients developed severe abdominal pain on days 12, 13 and 25 after admission respectively, and subsequently underwent emergency ERCP. Two of these patients were diagnosed with acute cholangitis, whereas the other patient had acute pancreatitis confirmed by a markedly elevated serum amylase level. Endoscopic retrograde cholangiopancreatography findings are summarised in Table 3. Following ERCP, the diagnosis of biliary tract disease (other than gallstone) was made in 12 (20%) patients in total. There were six cases of bile duct stone, three of acute pancreatitis, two of acute cholangitis, and one case of dilated biliary tract only.

In patients with common bile duct stones or 'sludge' on ERCP (n=9), the biliary tract was dilated in five patients, borderline-sized in two patients, and normal in a further two patients. All except one patient demonstrated floating stones during ERCP examination. One patient, who developed fever and right upper quadrant pain on day 12 after admission, was found during the emergency ERCP procedure to have an impacted ductal stone. Spontaneous passage of a ductal stone was diagnosed in one patient who had a dilated biliary tree and a loose papilla. Two patients with asymptomatic pancreatitis had a borderline-dilated common bile duct, but no obstructive lesion was identified.

Acute pancreatitis in patients with non–A-E hepatitis

A markedly elevated serum amylase level (greater than 1000 IU/L) was found in three patients (Table 3). None of these patients had fever, severe epigastric pain, or abdominal tenderness on admission. One of the patients subsequently developed a temperature of 38.3°C and severe abdominal pain, 2 weeks after admission. Abdominal ultrasonography in this case showed a dilated common bile duct and urgent ERCP was subsequently performed. Endoscopic retograde cholangiopancreatography revealed a dilated biliary tree and the presence of a gallstone. The other two patients had ultrasound findings of a dilated biliary tract and gallstone. The ERCP examinations revealed a borderline-sized biliary tree, without a ductal stone, in both cases.

Comparison of non–A-E hepatitis patients with and without biliary tract disease

Table 4 summarises the demographic data and laboratory results of patients with non–A-E hepatitis, with and without biliary tract disease (other than gallstone). Biliary tract disease tended to occur more commonly in female patients of older age but this finding was not statistically significant. Patients with biliary tract disease had a significantly shorter prothrombin time and lower serum ALT levels, and there was a trend towards higher serum albumin levels and higher platelet counts in this patient group.

In 61 patients with acute non–A-E hepatitis, multivariate analysis with logistic regression by forward stepwise technique was applied to the following factors: age, sex, white cell count, platelet count, prothrombin time, serum albumin level, serum globulin level, bilirubin level, serum alkaline phosphatase, and ALT level. The age, sex, serum albumin and ALT levels were the only independent predictors of biliary tract diseases (Table 5). There was no collinearity among the independent variables which were selected in the final model. The regression equation was as follows:
Prob (biliary tract diseases) = $e^{\beta'\chi} / 1 + e^{\beta'\chi}$ where
$\beta'\chi$ = -13.279 + 0.073 (age) - 0.001 (ALT) + 0.0264 (albumin) - 0.853 (sex)

Clinical outcomes

None of the patients with acute non–A-E hepatitis and normal ultrasound findings developed acute cholangitis, hepatitis, or biliary colic, during a median follow-up period of a year. All patients with confirmed biliary tract disease remained asymptomatic after papillotomy and/or complete removal of common bile duct stones.

Discussion

Despite the stringent clinical and laboratory criteria used for excluding patients with acute cholangitis or

Table 4. Comparison of demographic data and laboratory results in non–A-E hepatitis patients with and without biliary tract disease

	Non–A-E hepatitis		P value
	Biliary tract disease (n=12)	No biliary tract disease (n=49)	
Demographic data			
Sex (M/F)*	5/7	35/14	0.087
Age†	43 (26-71)	34 (16-73)	0.080
Haematological results†			
Haemogoblin (g/L)	139 (96-159)	143 (127-193)	0.236
White cell count ($x10^9$/L)	8.2 (5.3-14.3)	6.2 (4.2-17.4)	0.128
Platelet count ($x10^9$/L)	246 (167-374)	155 (134-246)	0.084
Prothrombin time (seconds)	10 (10-14)	11 (10-32)	0.015
Liver function tests†			
Albumin (g/L)	41 (38-48)	39 (31-49)	0.056
Globulin (g/L)	33 (28-47)	33 (21-55)	0.338
Bilirubin (mmol/L)	102 (28-221)	117 (8-637)	0.539
Alkaline phosphatase (U/L)	233 (134-389)	190 (65-573)	0.980
Alanine aminotransferase (U/L)	927 (407-2950)	1440 (400-6496)	0.036
Serum amylase (U/L)	92 (33-3408)	85 (14-988)	0.816

* Comparison by Fisher's Exact test. All other comparisons were made by Mann-Whitney U test
† Results are expressed as median (range)

Table 5. Multiple logistic regression analysis

Predictive factors	Regression coefficient	P value
Age	0.073	0.034
Sex*	-0.853	0.043
Serum alanine aminotransferase level (U/L)	-0.001	0.039
Serum albumin level (g/L)	0.264	0.029
Constant	-13.279	0.018

* If sex is male, value is 1, otherwise it is 0.

biliary obstruction, 20% of patients with a presumptive diagnosis of acute non–A-E hepatitis had biliary tract disease. Compared to patients with acute A to E hepatitis, patients with non–A-E hepatitis tended to be older, with higher white cell counts and lower serum ALT levels. After excluding patients with biliary tract disease from the analysis, however, the differences between these two groups on demographic variables and laboratory results were not statistically significant (data not shown). The results also suggested that acute viral hepatitis affects the male sex predominantly and usually occurs among a relatively younger age group.

Patients with non–A-E hepatitis, unrelated to biliary tract disease had significantly higher serum ALT levels and relatively prolonged prothrombin times, and showed a trend towards lower albumin levels. This suggests that non–A-E hepatitis, which is unrelated to biliary tract disease, might cause more severe hepatic injury, with synthetic functions of the liver impaired to a greater degree. Multivariate analysis using logistic regression, showed that serum ALT and albumin levels, together with age and sex were independent predictors for biliary tract disease in the study population. Interestingly, serum alkaline phosphatase level carried no predictive value in this study. This might be a reflection of exclusion criteria used in this instance. The question that arises from the current findings is whether biliary tract disease caused the liver impairment presenting as acute hepatitis in some cases, or whether it was merely coincidental.

The possibility of a coincidental finding cannot be excluded in view of the fact that 17% to 43% of patients with symptomatic gallstone disease had associated bile duct stones.[22-24] The temporal sequence of three patients, who initially presented with acute hepatitis and subsequently developed clinical features of biliary obstruction after a delay of 12 to 25 days, suggests that bile duct stones were the cause of the initial liver derangement in those cases. It would, however, be useful to detect the frequency of silent gallstones in patients with documented A to E viral hepatitis as a comparison.

Markedly elevated serum ALT levels have been reported in patients with extrahepatic biliary disease and biliary pancreatitis.[14,15,25] Hepatic histology of these patients showed acute inflammatory hepatocyte necrosis, hepatocyte degeneration, and acute cholangitis.[15,25] It was postulated that the liver cell injury seen was caused by acute bile duct obstruction, due to an impacted stone.[15] Mossberg and Ross[14] have suggested that bile duct obstruction could provoke augmented hepatic production and/or release of ALT, with leakage of the enzyme from grossly intact hepatocytes.[26] In contrast with the patients in the current study, all of

those patients had clinical evidence of acute cholangitis or severe abdominal pain suggestive of acute pancreatitis.

In this study, three patients in the biliary tract disease group had a borderline-sized or dilated bile duct without a stone, which may be due to the spontaneous passage of a stone. Of nine patients with bile duct stones, all except one patient had floating stones and only five patients had an obviously dilated common bile duct. Hence, it is hypothesised by the authors that transient biliary obstruction led to temporary liver damage. As the obstruction was transient and incomplete, bacterial infection had not yet developed. Thus clinical features of acute cholangitis were not observed.

The incidence of biliary tract disease in acute non–A-E hepatitis may have been underestimated in this study. Although the majority of bile duct stones migrate from the gallbladder, and thus are associated with gallstone, stones can arise de novo from the bile duct (primary stone). Primary bile duct stones are commonly seen in Asian countries, including the Hong Kong region,[27] and are typically associated with biliary infections,[17] and intrahepatic stones.[28] In the present study, ERCP was offered to patients only if abdominal ultrasonography indicated the presence of gallstones and/or an abnormal biliary system. The sensitivity of ultrasound in detecting both dilated intrahepatic biliary ducts and intrahepatic stones is lower than 70%,[29] and may be as low as 8% to 40% for common duct stones.[19,30] Primary stones could thus have been missed.

Conclusion

Biliary tract disease was found in 20% of patients with acute non–A-E hepatitis in this study. Age, sex, serum ALT level, and serum albumin level were the four independent predictive factors for biliary tract disease identified. Serum amylase levels and abdominal ultrasonography should be undertaken for all patients with acute non–A-E hepatitis. Findings of the current study indicate that ERCP is appropriate for those with gallstone and/or an abnormal biliary tract on abdominal ultrasonography. Whether ERCP is warranted for all patients with acute non-A-E hepatitis is an issue requiring further investigative studies.

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