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Predicting gallstone pancreatitis in HIV infected patients

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Background: Human immunodeficiency virus (HIV) infection, low cluster of differentiation (CD)4 counts and antiretroviral therapy can cause cholestasis and raised transaminases. In acute pancreatitis, this may render biochemical predictors of a gallstone aetiology inaccurate.
Methods: In a prospective observational study, acute pancreatitis was diagnosed by standard criteria. Cholecystolithiasis and bile duct diameter were diagnosed by ultrasound. Cholestasis was defined as two of the following: bilirubin ≥ 21 umol/l, γ glutamyl transferase ≥ 78 U/l, alkaline phosphatase ≥ 121 U/l. Cholangitis was defined as cholestasis and any two sepsis criteria: (temperature > 38˚C, WCC > 12.6 $\times 10^9$/L, pulse > 90 beats/min). Cholangitis, cholestasis, and bile duct diameter greater that 1 cm were indications for endoscopic retrograde cholangiopancreatography (ERCP). These parameters' ability to predict gallstone pancreatitis (GSP) and choledocholithiasis were compared in HIV+ve and HIV-ve patients.
Results: Sixty-two (26%) of 216 patients had GSP. Twenty four were HIV+ve patients. More HIV+ve patients had cholestasis ($p = 0.059$) and ERCP ($p = 0.004$). In HIV+ve patients alanine aminotransferase (ALT) > 100 U/L, gamma glutamyl transferase (GGT) > 2 upper limit of normal and cholestasis had a negative predictive value of 92%, 96.7% and 95.2% respectively. In HIV-ve patients, negative predictive value (NPV) was 84%, 83.8% and 84.6% respectively. Bile duct stones were demonstrated at ERCP in 6 (25%) and 3 (8%) of HIV+ve and HIV-ve patients respectively ($p = 0.077$). Five of 14 ERCP patients had no bile duct stones. HIV+ve and HIV-ve groups had two deaths each.
Conclusion: Absence at presentation of the abnormal parameters analysed were good predictors of a non-gallstone aetiology particularly in HIV+ve patients. Prior, magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) would reduce the number of non-therapeutic ERCPs.
Keywords: HIV infection, biochemical markers, gallstone related pancreatitis

Introduction

Biochemical markers in acute pancreatitis may aid in the prediction of a biliary aetiology and indicate the need for early interventions.[1-5] In some patients with pancreatitis and cholangitis, endoscopic retrograde cholangiopancreatography (ERCP) may be indicated. In those with cholecystolithiasis and cholestasis, evaluation for ductal stones is by abdominal ultrasound, magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS) or intraoperative cholangiography.[6-9] In previous studies a number of biochemical markers including total bilirubin (TBIL), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) alanine aminotransferase (ALT) and aspartate aminotransaminase (AST) have been investigated as markers of a biliary aetiology.[1,2,3]

In patients with human immunodeficiency virus (HIV) infection, there are several factors alone or in combination that may impact on these predictors of a gall stone aetiology and the possible need for ERCP. These factors may result in abnormal liver enzymes and biliary dilatation. Biliary tract abnormalities in HIV infection may be due to the same causes as in the HIV-ve population, e.g., choledocholithiasis and acalculous cholecystitis or as a result of HIV-related cholangiopathy (papillary stenosis, intrahepatic and extrahepatic bile duct stricturing) compounded by hepatocellular damage from concomitant anti-retroviral therapy.[10-14] These abnormalities occur more frequently in patients with cluster differentiation (CD)4 counts < 200.[4]

This study was performed to assess the prevalence of HIV infection in patients with gallstone pancreatitis (GSP) and to compare the ability of biochemical markers to predict GSP from other causes of acute pancreatitis (AP).

Patients and methods

From August 2013 to October 2015, a prospective evaluation of all patients with acute pancreatitis presenting to two regional hospitals in the Durban metropolitan area was performed. These hospitals serve underprivileged communities living in in their catchment area who are South African of African ancestry or South African of Indian ancestry. HIV status was ascertained from all those who consented to testing. HIV was diagnosed by two serial rapid third generation tests and an ELISA test was used in instances of discordant tests or rapid test results that were weakly positive. The Advanced Quality™ Rapid Anti-HIV (1&2) Test (InTec PRODUCTS INC, China) was used as

a screening test and the ABON™ HIV 1/2/0 Tri-line Rapid test (ABON Biopharm Hangzhou Company Ltd, China.) was used as the confirmatory test.

Acute pancreatitis was diagnosed by typical clinical symptoms (epigastric pain, nausea and vomiting) and three times the upper limit of normal of amylase (312 U/L) or lipase (180 U/L). Alcohol use was determined from the history. Temperature and pulse were recorded and white cell count, liver function tests, and C-reactive protein performed at presentation. In addition, the APACHE score was calculated. CD4 values were determined in all patients with HIV infection. Cholestasis was defined as the presence of any two of the following criteria: TBIL ≥ 21 µmol/l (normal range 5-21), GGT ≥ 78 U/L (normal range 0–39), ALP ≥ 121 U/L (normal range 42–98) and ALT ≥ 100 U/L (normal range 7–35 U/L). Patients with cholestasis were assessed for viral hepatitis. Cholangitis was defined as cholestasis plus any two of the following criteria: temperature > 38˚C, white cell count > 12.0 ×10⁹/L, pulse > 90 beats/min. Ultrasound was performed in all patients to confirm a gallstone aetiology and assess biliary dilation. ERCP was performed in patients with cholangitis, cholestasis and bile duct dilation > 1 cm. These parameters and their ability to predict GSP and choledocholithiasis were compared in HIV+ve and HIV-ve patients. In-hospital morbidity and mortality were recorded.

Statistics

Continuous variables were expressed as a mean and standard deviation and categorical variables as percentages. Differences in mean values were compared using student's t-test. Categorical variables were compared with the chi-square test (x^2) or Fisher's exact. A *p*-value of 0.05 was considered significant. The sensitivity, specificity, positive predictive and negative predictive values for a gallstone aetiology were calculated for the different markers and HIV status.

Results

From a cohort of 238 acute pancreatitis patients, accrued from August 2013 to October 2015, 22 had an unknown HIV status. Table I details the comparison of parameters between the 216 evaluable HIV+ve and HIV-ve patients. Sixty-two (26%) had GSP, 24 of whom were HIV+ve. Ninety-two per cent of patients in the HIV +ve group were female compared to 68% in the HIV-ve group. The HIV +ve group was a decade younger and 10/24 HIV+ve patients (41.7%) were on highly active antiretroviral therapy (HAART). C-reactive protein (CRP) values were lower in the HIV+ve patients than the HIV-ve patients ($p = 0.058$). The APACHE II score ≥ 8 was significantly higher in HIV+ve group than the HIV-ve ($p < 0.001$). Of the 24 HIV+ve patients, 22 had cholestasis compared to 26/38 HIV -ve ($p = 0.059$) Bile duct stones were demonstrated in 6/24 (25%) and 3/38(8%) of HIV+ve and HIV-ve patients respectively ($p = 0.077$). There was no significant difference in the morbidity and mortality rates in the two groups.

In the subgroup of patients on HAART, 90% were positive for the biochemical markers of biliary pancreatitis but this was not significantly different from patients not on HAART ($p = 0.3408$). The liver enzymes were raised in all 15 of those with CD4 counts > 350 cells/mm³ and in 8 of 9 with CD4 counts < 200cells/mm³ ($p = 0.4$). In Table II the accuracy of the biochemical predictors of a gallstone aetiology is assessed in HIV+ve and HIV-ve patients. In HIV+ve patients an ALT value of > 100 U/L, a GGT 2 × ULN (78 U/L) and cholestasis had negative predictive values (NPVs) of 91.5 (80.6–96.8), 96.7 (80.9–99.8) and 95.2 (82.6–99,2) respectively. In HIV-ve patients the NPVs were 84 (74.7–90.5), 83 (71–91.1), 84.6 (74.3–91.5) respectively.

Discussion

This study demonstrates, in patients with AP, a 38% prevalence of HIV infection which is more than 18% reported in the same metropole in 2017.[15] During the same

Table I: Comparison of characteristics of gallstone pancreatitis between HIV+ve and HIV-ve patients

Characteristic		HIV+ve (*n* = 24)		HIV-ve (*n* = 38)		*p* - value
Age		Mean	SD	Mean	SD	0.003
		35.1	8.3	45.4	14.8	
		n	**%**	***n***	**%**	
Gender	Female	22	91.7	26	68.4	0.059
	Male	2	8.3	12	31.6	
Severity	CRP > 150 mg/l	6	25.0	18	47.4	0.058
	APACHE II ≥ 8	19	79.2	7	18.4	< 0.001
Biliary	Cholestasis+	22	91.7	26	68.4	0.059
	Cholangitis+	7	29.2	8	21.1	0.467
	ERCP	10	41.7	4	10.5	0.004
	BD stones	6	25.0	3	8.0	0.077
Morbidity	Ascites	2	8.3	4	10.5	1
	Pseudocyst	2	8.3	3	7.9	1
	Abscess	1	4.2	1	2.6	1
	PVT	0	0	1	2.6	1
	PN	2	8.3	2	5.3	0.637
Mortality		2	8.3	2	5.3	0.637

Cholestasis: BR ≥ 21µmol/L, γ glutamyl transferase ≥ 78 U/L, alkaline phosphatase ≥ 121 U/L
Cholangitis: cholestasis+ any two of (temp > 38˚C, WCC > 12.6 ×10⁹/L, pulse > 90 beats/min)
PVT – portal vein thrombosis, PN – pancreatic necrosis

Table II: Diagnostic accuracy of biochemical markers in determining a gall stone aetiology in HIV+ve and HIV-ve patients with acute pancreatitis

Variable	Gallstone			Non-gallstone			Sensitivity	Specificity	PPV	NPV
	HIV+ve	%	HIV-ve	HIV+ve	%	HIV-ve				
	n		*n*	*n*		*n*	Per cent and (CI)			
	24		**38**	**66**		**88**				
ALT>100										
HIV+ve	19	79.2		12	18.2		79.2 (57.2-92)	81.8 (70-89.8)	61.3 (42.3-77.6)	91.5 (80.6-96.8)
HIV-ve		60.5	23		10.2	9	60.5 (43.5-75.5)	89.8 (81-94.9)	71.9 (53-85.6)	84 (74.7-90.5)
GGT>2×ULN(> 78 U/L)										
HIV+ve	23	95.8		37	56.1		95.8 (76.9-99.8)	43.9 (31.9-56.7)	38.3 (26.4-51.8)	96.7 (80.9-99.8)
HIV-ve		73.7	28		44.3	39	73.7 (56.6-86)	55.7 (44.7-66.1)	41.8 (30-54.4)	83 (71-91.1)
Cholestasis										
HIV+ve	22	92.7		26	39.4		91.7 (71.5-98.5)	60.6 (47.8-72.2)	45.8 (31.6-60.7)	95.2 (82.6-99.2)
HIV-ve		68.4	26		25	22	68.4 (51.2-82)	75 (64.4-83.3)	54.2 (39.3-68.3)	84.6 (74.3-91.5)

time interval, the frequency of gallstones as aetiology in HIV+ve patients with AP has increased only marginally from 24% to 27%.[15] The patients with HIV-related GSP were also significantly younger than HIV-ve patients, which has not been previously described.

Liver enzymes have been extensively evaluated as predictors of a biliary cause of AP. These evaluations are hampered by the heterogeneity of aetiologies and the variable timing and cut-off values used for markers of cholestasis and hepatitis.[6-8] Previous reports suggest that biliary, liver and pancreatic pathology may occur more frequently in HIV infected individuals leading to elevated liver and pancreatic enzymes.[16-18] This may compromise prediction of a gallstone aetiology and the need for further investigation or intervention.

In a study of 301 HIV+ve patients with abnormal liver enzymes, liver biopsies were compatible with drug-induced liver injury (42.2%), granulomatous inflammation (29%), steatosis/steatohepatitis (19.3%), coinfection with hepatitis B and C (22.3%) and overlapping pathologies in 16.2%.[12] HAART is associated with pathological changes in the liver, biliary tree and the pancreas but raised liver enzymes are not confined to those on treatment. Shiferaw et al. reported on 33 patients receiving HAART and 36 not on HAART.[11] The proportions with elevated ALT, AST, or both were 13%, 15.2% and 8.5% respectively and were not different between those receiving HAART and those who were treatment naive. They also found that patients with CD4 count < 200 cells/mm^3 were twice as likely to have raised liver enzymes than those with CD4 count > 350 cells/mm^3.[11] In this study, such a difference was not found. These elevations may also be due to acute hepatitis, drug interactions or concurrent alcohol intake.[12,17,18]

Imaging may be helpful in determining the aetiology of cholestasis. The yield of sonography in a matched study of 900 African adults with and without HIV found, in contrast to this study, significantly fewer gallstones in the HIV+ve positive group (23% vs. 75%). However, there were significantly more biliary ductal abnormalities of dilatation and wall thickening (25% vs. 12%) in the HIV+ve group.[16] The yield of magnetic resonance imaging (MRI) and MRCP was investigated in 31 HIV+ve patients with cholestasis, and showed 23 with multiple small gallstones, bile duct dilation or pancreatitis.[14] It is important to be aware of and exclude these pathologies in patients with HIV associated pancreatitis when utilising liver biochemistry to predict gallstones as an aetiology for the pancreatitis.

Trans-ampullary migration of gallstones may cause pancreatitis and cholestasis with elevated ALP, GGT and TBIL. Cholestasis was present in over 90% of HIV+ve patients and 68.4% of HIV-ve patients, yet the rate of cholangitis was similar. The presence of bile duct stones on ERCP in this study was threefold higher (25% versus 8%) in HIV+ve patients than in HIV-ve patients. We have previously reported a similar finding when evaluating patients who had cholecystectomy for symptomatic gallstones where we found patients who were HIV+ve to have a significantly higher frequency of cholestasis.[18]

In initial studies assessing biochemical parameters a cut-off point of twice the upper limit of normal, GGT had a positive predictive value of 92% in discriminating a biliary from a non-biliary cause of acute pancreatitis when performed on 84 patients at admission.[19] The predictive value of the transaminases may depend on the timing of the assay after onset of symptoms as ALT within 24 hours had a sensitivity, specificity and positive predictive value of 73%, 86% and 92% respectively. These levels of prediction are significantly reduced at 72 hours.[20]

Biochemical markers can be normal or elevated less than 3 × ULN in 10.4% to 26.4% patients with biliary pancreatitis.[1,21] Female gender, age of more than 50 years and amylase levels of more than 1000 IU/L may then provide pointers to a biliary cause. This was demonstrated in a study which investigated the predictive role of alkaline phosphatase > 300 IU/1, age > 50 years, ALT > 100 IU/1, female gender and amylase > 4000 IU/I. A combination of 3 or more of these factors was highly predictive of a biliary cause. When all five were present, all patients had a biliary cause of acute pancreatitis.[1] Despite potential limitations to the use of ALT in HIV+ve patients, we found ALT > 100 IU/L

was effective in predicting gallstone related pancreatitis. ALT and GGT > 100 U/L and female gender were associated with gallstone pancreatitis whereas advancing age was not.

Previous studies in HIV-ve patients that examined the presence of bile duct stones in patients with GSP have reported a large variation in prevalence rates. The number with bile duct stones at ERCP in the HIV-ve GSP group in the present study (8%) is comparable to the 11.5% based on intraoperative cholangiography reported in patients with GSP who were not assessed for their HIV status.[22] Navarro-Sandoz et al., in 134 GSP patients who had single stage laparoscopic management of their gall stones, found bile duct stones in 17%.[6] They also found that if the operation occurred after 30 days that the frequency of bile duct stones was half that of those operated on in under 30 days. This temporal difference in the prevalence of bile duct stones when imaged at different periods after initial presentation was confirmed in a study by Aranovich et al.[8] They found 11 patients had CBD stones on MRC out of 78 patients admitted GSP. Fourteen per cent were detected during the first 10 days from admission, 3.5% between 11 and 20 days and 1.8% between 21 and 30 days.

In this study, no temporal data was obtained on repeat liver function test or the date of ERCP, and we recognise that this is a limitation of our dataset. The absence of such data and the facts – that the primary author had no control over the adherence to the ERCP criteria, and 5 of the 15 patients had no stones detected has led us to recommend as others MRCP or EUS prior to ERCP.[7,9]

Conclusions

The low patient numbers with GSP in this series allows only inferences to be made regarding the trends observed. Morbidity and mortality were low and similar in HIV+ve and HIV-ve patients. The majority of HIV-infected individuals with GSP have deranged liver function tests, ALT, GGT and cholestasis above the threshold values. Absence of abnormal parameters in this series were good predictors of a non-gallstone aetiology particularly in those who were HIV+ve. The trend towards more bile duct stones in HIV+ve patients needs validation in larger series. MRCP or EUS should be performed prior to ERCP to reduce the number of non-therapeutic procedures.

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Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

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