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RAPID COMMUNICATION

Acute pancreatitis in acute viral hepatitis

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Abstract

AIM: To elucidate the frequency and characteristics of pancreatic involvement in the course of acute (nonfulminant) viral hepatitis.

METHODS: We prospectively assessed the pancreatic involvement in patients with acute viral hepatitis who presented with severe abdominal pain.

RESULTS: We studied 124 patients with acute viral hepatitis, of whom 24 presented with severe abdominal pain. Seven patients (5.65%) were diagnosed to have acute pancreatitis. All were young males. Five patients had pancreatitis in the first week and two in the fourth week after the onset of jaundice. The pancreatitis was mild and all had uneventful recovery from both pancreatitis and hepatitis on conservative treatment. The etiology of pancreatitis was hepatitis E virus in 4, hepatitis A virus in 2, and hepatitis B virus in 1 patient. One patient had biliary sludge along with HEV infection. The abdominal pain of remaining seventeen patients was attributed to stretching of Glisson's capsule.

CONCLUSION: Acute pancreatitis occurs in 5.65% of patients with acute viral hepatitis, it is mild and recovers with conservative management.

Key words: Acute hepatitis; Pancreatitis; Viruses; Pain; Abdomen

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INTRODUCTION

Although hepatitis viruses have a strong tropism for hepatocytes, viral antigens have also been detected in other tissues such as the pancreas and gallbladder[1,2]. Several viral infections have been implicated as an aetiological factor of acute pancreatitis. The viruses most frequently responsible are mumps virus, Coxsackie B virus, Epstein-Barr virus and measles virus[3-6].

Acute pancreatitis is not uncommon in fulminant hepatic failure (FHF) and has been confirmed based on histology or serology[7-9]. Acute pancreatitis has been reported very rarely in acute (nonfulminant) viral hepatitis. It has been reported with hepatitis A (HAV), hepatitis B (HBV) and non-A-non-B (blood-borne) and hepatitis E virus (HEV) infection[10-20].

The aim of this study was to determine the frequency and characteristics of pancreatic involvement in the course of acute viral hepatitis.

MATERIALS AND METHODS

Materials

Patients seen at the gastroenterology clinic and ward of SMS hospital, Jaipur between January 2004 and December 2006 were included in this prospective study. Acute viral hepatitis was defined as patients with prodromal symptoms, deep jaundice, markedly raised transaminases, presence of markers of hepatitis B (positive for HBsAg, IgM anti-HBc, HBeAg, but negative for anti-HBe), hepatitis A (IgM anti-HAV), hepatitis C (anti-HCV), hepatitis E (IgM-anti-HEV) viruses in serum and ultrasound abdomen showing thick walled gallbladder and hypoechoic liver. Patients with other causes of acute hepatitis, chronic liver disease, history of alcohol intake and fulminant hepatic failure were excluded from the study.

The diagnosis of acute pancreatitis was based on pancreatic type abdominal pain, raised amylase and lipase levels to three times the upper limit of normal and ultrasound (US) or contrast enhanced computed tomography (CECT) of abdomen suggestive of acute pancreatitis.

Methods

The acute viral hepatitis group underwent hemogram, serum bilirubin, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum alkaline phosphatase, prothrombin time, HBsAg, IgM anti-HBc, HBe Ag, anti-HBe, IgM anti-HAV, anti-HCV, IgM anti-HEV and ultrasound abdomen. Serum amylase and lipase, US of the abdomen and/or CECT were done in patients who had severe abdominal pain. Informed consent was obtained from each patient.

Table 1 Clinical and laboratory characteristics of 124 patients of acute viral hepatitis

	Acute viral hepatitis A (n = 16)	Acute viral hepatitis B (n = 54)	Acute viral hepatitis E (n = 54)
Male: Female	13:3	42:12	39:15
Age (yr)[1]	18.3 (8-35)	36 (20-74)	33.6 (17-62)
Clinical features			
Jaundice	15 (93.8)	54 (100)	54 (100)
Prodromal symptoms	16 (100)	54 (100)	54 (100)
Pain abdomen	4 (25)	8 (14.8)	12 (22.2)
Pruritis	4 (25)	9 (16.6)	19 (35.2)
Hepatomegaly (%)	6 (37.5)	16 (29.6)	21 (38.9)
Splenomegaly (%)	2 (12.5)	6 (11.1)	5 (9.2)
Hemoglobin (gm/dL)[1]	12.3 (9.6-14.5)	12.4 (9-15.1)	12.6 (9-14.7)
Platelets ($\times 10^5/mm^3$)[1]	2.5 (1.8-3.2)	1.8 (1.2-2.5)	1.6 (1-3.4)
Total leucocyte count ($\times 1000/mm^3$)[1]	7.9 (6.4-10.5)	8.4 (5-10.1)	7.2 (6-10.6)
Bilirubin (mg/dL)[1]	9.4 (0.67-35.8)	12.4 (3-36.5)	10.7 (3.3-26.3)
AST (IU/L)[1]	1969 (60-7715)	824 (223-3600)	1621.1 (240-3684)
ALT (IU/L)[1]	2134.3 (56-5165)	1024 (489-4900)	1830.6 (240-5549)
Serum alkaline phosphatase (IU/L)[1]	521.9 (196-1426)	424.5 (110-860)	324 (114-647)
Protein/Albumin (gm/dL)[1]	7.2 (6.5-7.8)/4.0 (3.5-4.6)	7 (6-8)/3.9 (3.4-4.8)	6.5 (5.5-8)/3.8 (3.4-4.6)
Prothrombin time prolongation[1]	4 (2-14)	5.5 (1-11)	6 (3-18)
Ultrasonography of the abdomen			
Thickened gallbladder	14 (87.5)	38 (70.4)	44 (81.5)
Hypoechoic liver	8 (50)	24 (44.6)	26 (48.1)
Gallbladder sludge	2 (12.5)	2 (3.7)	3 (5.5)
Ascites	1 (6.25)	3 (5.5)	26 (48.1)
Bulky pancreas	2 (12.5)	1 (1.8)	4 (7.4)

[1]Mean (range).

RESULTS

We had 124 patients with acute viral hepatitis over the three-year period, consisting of 94 males and 30 females, with a mean age of 32.7 years (range 8-65). The viral serology assays showed HBsAg and IgM-anti-HBc in 54 patients, IgM anti-HEV in 54 and IgM anti-HAV in 16 (Table 1). Twenty-four patients (19.4%) presented with history of severe abdominal pain, and 7 of these (29.2%) had evidence of acute pancreatitis. So, 5.65% of patients with acute viral hepatitis presented with acute pancreatitis. In the remaining 17 patients, the amylase and lipase were less than three times the upper limit of the normal. They did not have evidence of acute (calculous or acalculous) cholecystitis. We attributed the abdominal pain to stretching of the Glisson's capsule.

The clinical, laboratory and radiological profile of the patients with acute pancreatitis is given in Tables 2 and 3. The mean age was 23.9 (range 11-32) years, all were males. Abdominal pain occurred 2-30 (mean 12) days after the onset of jaundice. The duration of abdominal pain ranged from 24 to 120 h. None of the patients had a past history of jaundice, abdominal pain, alcoholism, trauma, hyperparathyroidism or drug intake. All patients had jaundice at presentation, mild hepatomegaly and epigastric tenderness. Three patients also had features of ileus.

On investigation, mean bilirubin was 16.4 mg/dL (range 5.8-32.4 mg/dL), mean AST 519 (range 182-1313) U/L and mean ALT 1371.1 (range 702-2438) U/L. Amylase and lipase ranged from 275-596 (mean 364.6) U/L and 520-7258 (mean 2495.4) U/L respectively. Serum lipid profile and calcium levels were normal in all patients. IgM anti-HEV, IgM anti-HAV, IgM anti-HBc were positive in 4, 2 and 1 patient respectively. US could detect pancreatitis in three patients, minimal ascites and biliary sludge in one patient. An abdominal CECT showed edematous and enlarged pancreas in all patients. There was no evidence of necrosis. The patient with sludge showed complete resolution in 2 wk. None of the other patients had evidence of biliary sludge during follow-up. The pancreatitis and hepatitis responded to conservative treatment in all patients. All patients are asymptomatic after a mean follow-up of 12 (range 8-24) mo.

DISCUSSION

Most cases of acute pancreatitis due to hepatitis viruses had been reported in association with acute liver failure (ALF). In the autopsy series of Ham and Fitzpatrick, 14 of the 42 (33%) patients with ALF had acute pancreatitis[8], the majority being of viral etiology. Similar findings had been reported by Parbhoo *et al*[9] in 21 out of 59 patients (36%) with ALF who had acute pancreatitis. Autopsy findings of pancreatitis in seven of 16 (44%) patients with fulminant viral hepatitis, versus two of 33 (6%) patients with fulminant hepatic failure secondary to halothane, support the role of viral infection rather than liver failure per se in causing pancreatitis[21].

There are only a few case reports of symptomatic pancreatitis occurring in the setting of acute viral hepatitis[10]. Most of the patients reported had presented with symptomatic pancreatitis in the early phase of the hepatitic illness[11-20] whereas Mishra *et al*[10] reported 6 patients at wk 2 or 3 after the onset of jaundice. Our series had five patients presenting in the first week and two in the fourth week after the onset of jaundice. One patient had biliary sludge and presented in the first week of jaundice. Ultrasound was done weekly in all the patients until clinical and biochemical resolution. Gallbladder wall thickness

Table 2 Clinical Profile of viral hepatitis patients with acute pancreatitis

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (yr)	11	30	32	21	30	20	23
Gender	M	M	M	M	M	M	M
Pain interval after onset of jaundice (d)	30	28	3	2	5	6	5
Pain duration (h)	96	72	120	96	24	48	72
Hepatomegaly (cm; subcostal)	5	2	2	3	3	2	3
Etiology	Hepatitis A	Hepatitis B	Hepatitis E	Hepatitis E	Hepatitis E	Hepatitis A	Hepatitis E
Recovery from pancreatitis (d)	8	6	12	6	3	6	4
Recovery from hepatitis (wk)	8	6	12	8	8	12	10

Table 3 Laboratory profile of viral hepatitis patients with acute pancreatitis

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Bilirubin (mg/dL)	32.4	21.3	14.6	11.8	5.8	13.1	15.8
AST (IU /L)	682	1210	1313	182	388	1223	765
ALT (IU/L)	895	702	2238	702	412	2438	814
Alkaline phosphates (IU/L)	560	300	607	420	531	503	231
Albumin (mg/dL)	3.8	4	3.5	3.8	3.5	3.9	3.5
Prothrombin time prolongation (s)	14	11	12	9	11	10	18
Amylase (IU/L)	475	460	275	278	462	319	596
Lipase (IU/L)	7258	520	3297	990	760	2926	2060
Corrected Serum calcium (mg/dL)	9.2	9.1	9	8.9	9.2	9.3	8.1
Serum triglyceride (mg/dL)	140	168	131	165	141	160	154
Ultrasonography (Gallbladder)	Normal	Normal	Normal	Normal	Normal	Normal	Biliary sludge

(more than 3 mm) was found in 96.8% of patients, which is in agreement with a previous study by Sharma *et al*[22]. None of the two patients who presented later had any evidence of biliary sludge on US.

The etiology of pancreatitis was considered to be due to a hepatitis virus in all patients, as there was no evidence of gallstones, sludge, alcohol, drugs, trauma or metabolic causes. The remaining patient had biliary sludge on US. The disappearance of biliary sludge at 2 wk occurred a week later than previously reported[23]. None of the 7 patients with biliary sludge had an episode of acute pancreatitis and gallbladder contraction was similar in the hepatitis and control group in the Portincasa *et al*[23] group. So, the patient might had HEV-associated pancreatitis and had biliary sludge during the acute phase of the viral illness which resolved on follow-up ultrasound abdomen. Basaranoglu *et al*[24] reported a case of gallbladder sludge and acute pancreatitis induced by acute hepatitis A.

Acute pancreatitis in nonfulminant acute viral hepatitis covers the full range of clinical severity. Subclinical pancreatic involvement in viral hepatitis may occur more commonly than is appreciated[25]. The pancreatitis was mild as reported previously[10,13-20]. One of our patients had minimal ascites which resolved in 2 wk. There were no local or systemic complications and all had uneventful recovery from both pancreatitis and hepatitis. No relation was found between the level of amylase and severity of pancreatitis.

The frequency of acute pancreatitis in acute viral hepatitis in the present series is 5.65%, which is 2% higher than reported by Joshi *et al*[26] in their autopsy series of 108 cases. Joske *et al*[27] noted 8 cases of acute viral hepatitis out of 90 patients of acute pancreatitis.

The mechanism of pancreatitis in patients with acute viral hepatitis (nonfulminant) is unknown, and it may be multifactorial. One proposed pathogenesis of pancreatitis associated with hepatitis is the development of edema of the ampulla of Vater with obstruction to the outflow of pancreatic fluid[28]. There is no direct evidence for the routes by which hepatitis viruses reach the pancreas; however, the proposed routes are most likely blood or bile[14].

A more plausible mechanism for viral associated acute pancreatitis is direct inflammation and destruction of pancreatic acinar cell by the virus. This latter theory is supported by the autopsy finding of hepatitis B virus antigens within the cytoplasm of pancreatic acinar cells of patients with hepatitis B surface antigenemia[1,2]. It is possible that the severity of pancreatitis is related to the magnitude of exposure of pancreatic acinar cells to the hepatitis virus[2].

The hepatitis viruses might injure the pancreatic acinar cell membrane, resulting in the leakage of intracellular enzymes, and/or precipitate a network of intracellular events culminating in cell death by a mechanism analogous to hepatocyte necrosis[29]. Another mechanism can be the release and circulation of lysosomal enzymes from the inflamed liver with the activation of trypsinogen to trypsin.

When acute pancreatitis is associated with fulminant hepatitis, the virus may cause tissue damage directly, but there are several other factors which can play an important role in the development of pancreatitis (clinical or silent) and these include acute liver failure, hypotension, infections and drug induced damage[13]. Intrapancreatic

hemorrhage due to hypoprothrombinemia or disseminated intravascular coagulation may result in pancreatic damage and subsequent pancreatitis[8].

In conclusion, acute pancreatitis is not uncommon. In a patient with acute viral hepatitis and acute or disproportionate abdominal pain, acute pancreatitis should be kept as a possibility. Conservative treatment leads to recovery in all the patients.

COMMENTS

Background

The association of hepatitis viruses with acute pancreatitis in the setting of acute (nonfulminant) viral hepatitis is rare. The frequency and characteristics of pancreatic involvement in the course of acute viral hepatitis needs to be elucidated.

Research frontiers

Studies with larger number of patients of acute viral hepatitis with pain abdomen are necessary to determine the frequency and characteristics of pancreatitis as there are only case reports and one case series of six patients.

Innovations and breakthrough

Recent reports describe acute pancreatitis as a cause of acute or dispropionate abdominal pain complicating acute viral hepatitis.

Applications

Patients of acute viral hepatitis with severe pain abdomen should undergo serum amylase, lipase and ultrasonography or contrast-enhanced computed tomography of the abdomen to prove acute pancreatitis as a cause of abdominal pain. The prognosis of patients with acute pancreatitis in the setting of acute viral hepatitis is good and patients recover on conservative treatment.

Terminology

Acute viral hepatitis is defined as presence of prodromal symptoms, deep jaundice, markedly raised transaminases, presence of markers of hepatitis B (positive for HBsAg, IgM anti-HBc, HBeAg, but negative for anti-HBe), hepatitis A (IgM anti-HAV), hepatitis C (anti-HCV), hepatitis E (IgM-anti-HEV) viruses in serum and ultrasound abdomen showing thick walled gallbladder and hypoechoic liver . Patients with other causes of acute hepatitis, chronic liver disease, history of alcohol intake and fulminant hepatic failure were excluded from the study. The diagnosis of acute pancreatitis was based on pancreatic type abdominal pain, raised amylase and lipase levels to three times upper limit of the normal and ultrasound (US) or contrast enhanced computed tomography (CECT) of the abdomen suggestive of acute pancreatitis.

Peer review

This article describes the clinical findings of acute pancreatitis in acute viral hepatitis. The main content of the manuscript is good.

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