

## Acute pancreatitis in acute viral hepatitis

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### ABSTRACT

**Introduction:** The association of acute viral hepatitis and acute pancreatitis is well described. This study was conducted to find out the frequency of pancreatic involvement in acute viral hepatitis in the Nepalese population.

**Methods:** Consecutive patients of acute viral hepatitis presenting with severe abdominal pain between January 2005 and April 2010 were studied. Patients with history of significant alcohol consumption and gall stones were excluded. Acute viral hepatitis was diagnosed by clinical examination, liver function test, ultrasound examination and confirmed by viral serology. Pancreatitis was diagnosed by clinical presentation, biochemistry, ultrasound examination and CT scan.

**Results:** Severe abdominal pain was present in 38 of 382 serologically-confirmed acute viral hepatitis patients. Twenty five patients were diagnosed to have acute pancreatitis. The pancreatitis was mild in 14 and severe in 11 patients. The etiology of pancreatitis was hepatitis E virus in 18 and hepatitis A virus in 7 patients. Two patients died of complications secondary to shock. The remaining patients recovered from both pancreatitis and hepatitis on conservative treatment.

**Conclusions:** Acute pancreatitis occurred in 6.5 % of patients with acute viral hepatitis. Cholelithiasis and gastric ulcers are the other causes of severe abdominal pain. The majority of the patients recover with conservative management.

**Keywords:** acute viral hepatitis, acute pancreatitis, pain abdomen, hepatitis E, hepatitis A, endemic zone

### INTRODUCTION

Gallstones and alcohol are the most common causes of acute pancreatitis (AP). The role of infective agents as the etiology of AP remains controversial.<sup>1</sup> However, infective agents as a cause of AP was hypothesized as early as 1817.<sup>2</sup> The infective cause of AP was first documented by Lemoine as early as 1905.<sup>3</sup> He demonstrated pancreatitis in a patient with mumps infection. Mumps virus, coxsackie virus, adenovirus,

cytomegalo virus and herpes simplex virus have been reported as rare viral causes of AP in the literature.<sup>1,4,5</sup> Similarly, Balakrishnan et al found that patients with tropical pancreatitis more often had antibodies to the mumps virus and cytomegalovirus and less often had antibodies to rubella than healthy controls.<sup>6</sup> The association between viral hepatitis and AP was first reported in 1944 by Linsey.<sup>7</sup> In a retrospective review

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of autopsies, Joshi et al. noted that 3.7 % of patients with pancreatitis also had viral hepatitis.<sup>8</sup> In an Indian study, out of 334 cases of AP, seven patients were found to have acute viral hepatitis (AVH).<sup>9</sup> Thus, the single hepatotropic viral etiology causing two different diseases in a person has virtually been established at the present time. This study was carried out in Nepal, which is an endemic zone for AVH due to hepatitis E and A, to see the pancreatic involvement in patients of AVH. To the best of our knowledge, this study has included the largest number of patients compared to similar study carried out elsewhere.

## METHODS

We prospectively assessed the pancreatic involvement in cases presenting clinically with features of AVH and severe abdomen pain. Consecutive patients of AVH presenting in the Liver Unit of Bir Hospital and Norvic International hospital between January 2005 and April 2010 were included in this study. Acute viral hepatitis was diagnosed on the basis of the presence of prodromal symptoms, clinical examination, liver function tests, viral serology and ultrasound examination. All patients underwent a thorough clinical examination, blood tests for hemogram, liver function test, viral serology for HAV, HBV, HEV and HCV and ultrasound examination. Patients having less than a five-fold rise in serum transaminase and/or negative viral serology were excluded from the study. Patients with severe pain abdomen were admitted for observation, further evaluation and management. Those patients presenting with severe pain abdomen were subjected to a further blood test for serum amylase, serum lipase, renal function test, lipid profile and serum calcium. Contrast-enhanced CT scan of the abdomen was advised to all patients. An upper GI endoscopy was done when required. Acute pancreatitis was diagnosed on the basis of severe pain abdomen, a more than three-fold rise of serum amylase and imaging evidence of AP. Those patients with recent history of significant alcohol intake and evidence of cholelithiasis or the gall bladder lumen full of sludge were excluded from the study. Statistical analysis was done using SPSS ver. 10. Consent for the study was taken from all patients and the Institutional Review Board gave the permission for the study.

## RESULTS

A total of 428 clinically-suspected cases of AVH were seen in the OPD and emergency department in the four years of the study period. Forty-six patients were excluded because of negative serology or serum transaminase less than five times the upper level of the normal limit. The remaining 382 patients were enrolled in the study. The demographic profiles of the patients are given in Table 1. Of the 382 patients, the etiology

of the AVH was hepatitis E in 286 cases, hepatitis A in 78 cases and hepatitis B in 18 cases. The clinical presentation, laboratory findings and ultrasound findings are given in Table 2, 3 and 4 respectively. The biliary tree was specially focused in the USG examination of the AP patients. the intra-hepatic bile ducts were not dilated. With exception to one patient, the common bile duct diameter was less than 7.2 mm. The MRCP revealed no abnormality and no further test was carried out. The clinical findings were similar to the findings of our previous study.<sup>10</sup> A detailed of the analysis clinical finding of AVH is beyond the scope of this study. However, it is worth mentioning that 2 % of the patients were diagnosed to have acute liver failure. Of the 382 cases, 38 patients were admitted with complaints of severe pain abdomen. However, there were other cases of mild pain abdomen that were more related to liver swelling, gastritis or reflux esophagitis. The etiology of severe pain abdomen is given in Figure 1. Twenty-five of the 382 patients (6.5 %) suffering from AVH were diagnosed to have AP due to hepatotropic virus. Eight patients were found to have cholelithiasis. Pain was due to multiple gastric ulcers in two patients. In three patients, no apparent cause was seen. Out of three, two patients were found to have a thick gall bladder sludge that probably was the cause of the pain. In the remaining one patient, the cause of pain could not be ascertained. Due to the presence of periodic pain, the sphincter of Oddi dysfunction was suspected, but further tests were not possible in our set-up. These patients were excluded from the study. One patient was diagnosed to have concomitant acute liver failure and AP. The etiology of pancreatitis was hepatitis E virus in 18 and hepatitis A virus in 7 patients. The onset of severe pain was noticed 1 - 15 (mean 8.4) days of the onset of jaundice. Laboratory investigations of patients with AP are given in Table 5. A CT scan could be done in only 19 patients due to the affordability problem. Swollen pancreas, per-pancreatic fluid collection, collapsed gall bladder with or without sludge, ascites and effusion were most common findings. The typical findings of the USG and the CT scan are given in Figure 2 and 3. The USG could detect AP in 14 cases. All the patients were managed conservatively except for the one who had to undergo hemodialysis due to acute renal failure. Two patients died due to complications secondary to shock. Both of these patients had been referred from other centres. The remaining patients had an uneventful hospital stay. The mean duration of hospital stay was 10.4 days (range, 7-18 days). Serum amylase came to normal after the mean duration of 4.8 days (range, 3 - 10 days). Complete pain relief was attained after 2 - 12 days with a mean of 5.2 days. The patients of AVH were seen after one month of the diagnosis at the OPD. Since the LFT was within the normal limit, they were not asked for any follow-up. The patients of AP were

followed up after one week and four weeks. There was no clinical or biochemical evidence of residual illness. A follow-up USG was done in every patient after seven days of discharge. The clinical and sonological features of pancreatitis were absent in all the cases.

## DISCUSSION

Although hepatotropic viruses are known to cause hepatitis, their antigens are also demonstrated in other organs like the gall bladder and pancreas.<sup>11,12</sup> This may explain the appearance of pancreatitis in viral hepatitis. There has been histological evidence of AP in cases of acute liver failure.<sup>13,14,15</sup> However, in our study, only one out of 25 patients with AP was diagnosed to have acute liver failure. Ham and Fitzpatrick published an autopsy series of fulminant hepatic failure and found that the incidence of AP was 33 %.<sup>14</sup> The incidence of the same was 36 % in the case published by Parbhoo et al.<sup>15</sup> Mild sub-clinical pancreatitis has been described in non-fulminant AVH.<sup>16</sup>

Mishra et al published a series of 6 cases of non-fulminant viral hepatitis complicated by AP, including the first documented case of HEV-associated pancreatitis.<sup>17</sup> After that, a few more case reports have been published, predominantly from endemic regions. In a retrospective study from India, seven patients (2.09 %) were found to have AVH in patients diagnosed to have AP. To the best of our knowledge, this study has analyzed the largest number of patient so far. In our study 6.5 % patients of AVH presented with AP. Compared to a study by Jain et al,<sup>18</sup> the incidence of pancreatitis was high (5.6 % vs 6.5 %) in our study. Although our study population had similar demographic and other profiles, we had a higher rate of pancreatic involvement in our cases, the reason of which is unclear.

The mechanism of pancreatitis in patients with AVH is still unknown. A multifactorial mechanism may be responsible for its development. One proposed pathogenesis of pancreatitis associated with hepatitis is the development of AP secondary to direct inflammation

and destruction of pancreatic cells by the virus. This theory is supported by the fact that autopsy finding of hepatitis B virus antigen within the cytoplasm of pancreatic acinar cells of HBsAg-positive patients has been reported.<sup>19,20</sup> However, why only some people develop AP among HBsAg-positive patient is unexplained. It is possible that the severity of pancreatitis may be related to the extent of exposure of pancreatic acinar cells to the hepatotropic virus, its viral load and immune status of the patient. One of the plausible explanations is that the hepatotropic viruses might injure the pancreatic acinar cell membrane, resulting in the leakage of intracellular enzymes or by intracellular events resulting in cell death by a mechanism equivalent to hepatocyte necrosis.<sup>21</sup> Another mechanism proposed by Tsui et al is that there is development of edema of the ampulla of Vater with obstruction to the outflow of pancreatic fluid causing AP.<sup>22</sup> However, the pathogenesis of edema is not well described. Another mechanism can be the release and circulation of lysosomal enzymes from the inflamed liver with the activation of trypsinogen to trypsin.<sup>18</sup> When AP is associated with fulminant hepatitis, the virus may cause tissue damage directly, but here 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.

The diagnosis of occult pancreatitis that we didn't look for may be taken as one of the drawback of this study. The viral serology and genotype of the HAV and HEV could have given greater weight to the study and could have given an idea about which genotype is more associated with AP.

## CONCLUSIONS

This study suggests that a diagnosis of AP should be considered in a case of AVH in an endemic zone whenever patients present with severe pain abdomen. The majority of patients recover with conservative treatment if they present before there is circulatory abnormality.

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