HEPATITIS E VIRUS INFECTION IN CHRONIC LIVER DISEASE CAUSES RAPID DECOMPENSATION

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ABSTRACT

Hepatitis E previously known as enterically transmitted non-A, non-B hepatitis, is a self limiting infectious viral disease of developing countries. Various issues regarding the pathogenesis of liver injury and its natural history remain unanswered after two decades of its discovery. A small proportion of patients develop fulminant hepatic failure. Mortality is very high if it is associated with pregnancy, especially during third trimester. After establishment of hepatitis A virus as a cause of decompensation of chronic liver disease, now there are reports that hepatitis E viruses also does the same. Acute hepatitis E in these patients has a protracted course with high morbidity and mortality. Many patients develop hepatorenal syndrome, hepatic encephalopathy and even liver failure after co-infection with hepatitis E virus. Now time has come to institute hepatitis E virus superinfection as one of the cause of acute on chronic liver failure. Hepatitis E is a problem of developing countries and Nepal is in the endemic zone. Sudden decompensation in chronic liver disease patient, who were otherwise stable and under regular follow up, should be carefully dealt with. Patient statistics at our unit shows that 7 cases of chronic liver diseases with superinfection with hepatitis E virus were dealt from April 2004 to August 2005. Two patients (29%) died and 5 recovered. In patients with recovery, there was deterioration of Child-Pugh grading and the duration of hospital stay was longer. Thus, hepatitis E in diagnosed chronic liver disease case should be taken apprehensively. Similarly patients of chronic liver disease traveling to endemic zone should take precaution. If vaccine against hepatitis E virus is developed, chronic liver disease patient would be the eligible candidate for vaccination beside pregnant ladies.

Key Words: Hepatitis E, Chronic Liver Disease, Decompensation.
INTRODUCTION

Hepatitis E previously known as enterically transmitted non-A, non-B hepatitis, is an infectious viral disease with clinical and epidemiological features of acute hepatitis. It is a water-born disease, transmitted primarily by contaminated water. There is also a possibility of zoonotic spread of the virus, since several non-human primates, pigs, cows, sheep, goats and rodents are susceptible to the infection. Hepatitis E virus (HEV) is a major cause of enterically transmitted hepatitis worldwide.1,2 It is an important pathogen in Asia, the Middle East, and parts of Africa and Central America. This disease has been shown to occur in both epidemic and sporadic forms. Epidemic forms are primarily associated with the ingestion of fecally contaminated drinking water. It was first documented in New Delhi, India in 1955, when 29000 cases of icteric hepatitis were identified following widespread fecal contamination of city’s drinking water pipeline.3 In Kathmandu valley an epidemic of viral hepatitis was reported in 1973 involving 10000 cases. It was associated with high mortality rate in pregnant women.4 In developed countries outbreaks have not been reported. However, sporadic cases of HEV infection in persons returning from endemic areas are seen. The incubation period for HEV is 2 to 9 weeks (mean 6 weeks), and the spectrum of disease ranges from subclinical infection to fulminant hepatitis. Clinical features can include fever, chills, jaundice, dark urine, anorexia, nausea, vomiting, abdominal pain, headache, myalgia, and arthralgia.1,5,6,7,8 Few patients have a prolonged course with marked cholestasis.9 A small proportion of patients develop fulminant hepatic failure. Mortality is very high if it is associated with pregnancy, especially during the third trimester.4,7,8 Several questions regarding the pathogenesis of liver injury and its natural history remain unanswered two decades after the discovery of this virus. The prevalence of IgG anti-HEV antibodies among healthy blood donors in South Asia is around 18%.10

Acute superinfection with a hepatotropic virus is a well-recognized cause for worsening of chronic liver disease (CLD). In patients with chronic hepatitis B, hepatitis D virus superinfection is known to result in decompensation. Hepatitis A virus (HAV), another enterically-transmitted hepatotropic virus, has been shown to induce liver injury and decompensation among patients with CLD.13 HEV infection has classically been described as causing an acute and self-limiting illness and no clinical or histological evidence of chronic hepatitis or cirrhosis has been detected among patients with acute hepatitis E.3,10 The available data on the role of HEV infection in causing worsening of pre-existing CLD are limited.15 It has been reported that the incidence of anti HEV IgG amongst blood donors and patients with underlying CLD are almost similar.11 The importance of studying the natural history of superimposed HEV infection in CLD is highlighted by the fact that more than 80% patients of CLD are prone to this water-borne infection in endemic areas.10 Once superinfected, there is increased chance of decomposition of CLD.

Acute-on-chronic liver failure (ACLF) is described as acute deterioration in liver function over a period of 2 to 4 weeks in a person with previous liver disease of more than six-month duration.14 It is often associated with a precipitating event leading to severe deterioration in the clinical state, and usually presents with jaundice and hepatic encephalopathy and/or hepatorenal syndrome. These patients show a high Acute Physiology and Chronic Health Evaluation (APACHE) or Sequential Organ Failure assessment (SOFA) score. The pitfall of this definition, however, is its inability to cover minor deterioration.

Now it is evident that HEV superinfection is one of the major causes of decomposition or even ACLF in CLD patients.15 Patients of CLD present with severe hepatic dysfunction, as indicated by the presence of ascites in all and hepatic encephalopathy in most patients when superinfected by HEV. Hepatorenal syndrome develops in few patients and contributes to death.16 These observations are similar to the more severe hepatitis and high case-fatality rate reported in patients with acute HAV infection superimposed on chronic hepatitis B or C.17 Hamid et al reported 4 patients with CLD and HEV superinfection; one patient in their series died following renal failure and spontaneous bacterial peritonitis.15 In a study, it was found that the mortality rate in CLD patients was lower than those who did not have HEV infection. The decomposition in the latter group was possibly related to progression of the underlying disease. The mortality rate among patients (14%) was much higher than the mortality rate of 0.07% to 0.6% reported during large outbreaks of acute hepatitis E.18 In a study by Kumar et al it was found that HEV superinfection
was responsible for recent decompensation in 44% of studied CLD patients. Sallie et al reported a patient with fulminant liver failure caused by coexistent Wilson’s disease and hepatitis E; however, liver histology in this patient did not reveal any evidence of liver cirrhosis or fibrosis. Recovery of liver function test takes longer, not less than 2 months in CLD infected with HEV. In contrast, liver function recovers within 6 weeks in most adults with hepatitis E without underlying CLD.

**Our experience**

Our experience with HEV superinfection in CLD is limited. Patient statistics at our unit shows that there were 7 such cases from April 2004 to August 2005. Two patients (29%) died and 5 recovered. Case summaries of two patients are given below.

**Case 1**

A known case of cardiac cirrhosis and portal hypertension with grade II esophageal varices under regular medication and follow-up was admitted to our unit with complain of sudden distension of abdomen and yellowish discoloration of the eyes for 5 days. He gave history of flu like illness prior to development of yellowish discoloration of eyes. On examination, there were stigmata of CLD (spider naevi, loss of axillary hair, white nails, clubbing) and multi-valvular heart disease. Pulse and blood pressure were normal. Ascites was moderate and pedal edema was present. Laboratory report on admission showed total bilirubin 15 mg/dL, conjugated bilirubin 11 mg/dL, alanine transaminase 565/35 U/L, alkaline phosphatase 250/232 U/L, γ-GT was 190/61 U/L. Prothrombin time was 19/14 seconds and albumin 2.5 gm/dL. Anti HEV IgM was present and anti HA V IgM was absent. Peritoneal fluid showed 25 PMN cells/mm³ and there was no bacterial growth. Albumin in peritoneal fluid was 1.2 gm/dL. Peritoneal fluid showed no cells and no growth. Ascitic albumin was 1.6 gm/dL. Anti HEV IgM was present and anti HAV IgM was absent. Peritoneal fluid showed 25 PMN cells/mm³ and there was no bacterial growth. Albumin in peritoneal fluid was 1.2 gm/dL. Renal function was normal evident by normal urea and creatinine level. Ultrasound examination of abdomen showed dull edge of liver with inhomogeneous parenchyma. Right and middle hepatic veins were blocked by organized thrombus. Left hepatic vein opened to IVC via collateral at caudate lobe. IVC was narrowed near ostium of right and middle hepatic vein. Spleen was enlarged (length 11.5 cm, Splenic index 25 cm²). There was tortuous collateral vessel at splenic hilum. Upper gastrointestinal endoscopy showed 4 columns of grade II esophageal varices without red color signs. The patient was managed conservatively. During admission she developed grade IV hepatic encephalopathy probably precipitated by hospital acquired infection. Patient was managed by IV antibiotics, FFP transfusion and other conservative management was done. Patient improved and was discharged after 42 days of admission.

**Case 2**

A 32-year-old female was admitted with complaints of yellow eyes, loss of appetite, nausea and distension of the abdomen. She gave history of jaundice, two episodes, in past that was treated by Ayurvedic medicines. She also gave history of secondary amenorrhea. On examination, she was deeply icteric and abdomen was distended but flanks were not full while shifting dullness was positive. There was prominent vein in the anterior abdominal wall with flow from below upward. Liver was palpable (5 cm in right mid-clavicular line), firm in consistency, smooth surface and blunted edge. Spleen was palpable on left lateral position. Laboratory report on admission showed total bilirubin 33 mg/dL, conjugated bilirubin 25 mg/dL, alanine transaminase 865/35 U/L, alkaline phosphatase 454/232 U/L, γ-GT 81/61 U/L, prothrombin time 35/14 seconds and albumin 2.2 gm/dL. Peritoneal fluid showed no cells and no growth. Ascitic albumin was 1.6 gm/dL. Anti HEV IgM was present and anti HAV IgM was absent. Peritoneal fluid showed 25 PMN cells/mm³ and there was no bacterial growth. Albumin in peritoneal fluid was 1.2 gm/dL. Renal function was normal evident by normal urea and creatinine level. Ultrasound examination of abdomen showed no apparent space occupying lesion in the liver as well as thrombus in the portal vessels that may have deteriorated the condition. The patient was managed conservatively with IV antibiotics, albumin infusion, salt and fluid restriction. Patient felt better after initiation of treatment. Repeat liver function showed prolonged prothrombin time that was corrected by transfusion of fresh frozen plasma. The patient developed gradual decrease in urine output during hospital stay. Despite combination of different diuretics urine output gradually decreased to less than 150 ml/day and renal function test became abnormal. There was progressive rise of blood urea nitrogen and creatinine. Finally anuria developed in few days time and he was diagnosed as hepatorenal syndrome. Beside withdrawal of diuretics, treatment with octeotride (somatostatin analogue) plus albumin infusion was tried but renal failure did not improved. Upon request of patient party hemodialysis was also carried but without any success. Patient succumbed to renal failure on 45th days of admission.
SUMMARY

To summarize, superinfection with HEV in patients with underlying CLD causes severe liver decompensation that is frequently complicated with hepatic encephalopathy and renal failure ensuing ACLF. Hepatitis E infection, although a self-limiting disease, in this setting has a protracted course with high morbidity and mortality. Our experience also supports the fact that HEV shares this propensity of causing severe disease in patients with CLD. In case one, there was decompensation of CLD after HEV superinfection. Hepatorenal syndrome eventually developed and patient died within short span despite aggressive treatment. In case 2, patient’s CLD was diagnosed by the virtue of superinfection of acute HEV hepatitis. Otherwise stable CLD showed signs of decompensation due to HEV superinfection. Therefore, it is important to prevent HEV infection among patients with established CLD in HEV-endemic regions. Owing to mortality during pregnancy and increased mortality and morbidity in CLD patients, vaccine against HEV is sought after. At present, no commercially available vaccines exist for the prevention of hepatitis E. However, several studies for the development of an effective vaccine against hepatitis E are in progress. Once HEV vaccine is available, these patients may be good candidates for it, beside travelers of non-endemic region. In the meantime, such patients in HEV-endemic regions should be advised to take appropriate precautions to avoid contaminated food and drinks. In addition, patients with liver cirrhosis residing in non-endemic regions should take precautions while traveling to HEV-endemic regions.

REFERENCES