*Original article*

# Superinfection of hepatitis E Virus as a cause of decompensation in liver cirrhosis due to hepatitis B virus

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**Abstract**

**Objevtive**: Super infection with hepatitis A virus (HAV) and hepatitis E virus (HEV) in the presence of underlying hepatocellular injury can cause severe illness. In endemic areas such as India, however most patients already have been exposed to HAV but could still be susceptible to HEV infection. In our study we determined the seroprevalence of anti-HAV IgM and anti-HEV IgM to assess the incidence of superinfection with these viruses in cirrhotic patients with the goal of defining the need for protection against these viruses and further correlate the presence of these viruses with the clinical course. **Methods**: We studied 53 patients of cirrhosis as a result of Hepatitis B virus. Apparent causes of decompensation were ruled out before their inclusion in the study group. Serum sample from these patients was tested for HBsAg, anti HBc IgG, anti HEV IgM and anti HAV IgG and IgM by commercially available ELISA kit. Liver function test was done on all the patients and correlated with various serological markers. **Results**: anti HBc IgG was present in all the cases of cirrhosis. Hepatitis B surface antigen was present in 20 out of 53 cases of cirrhosis. None of the patients demonstrated anti-HAV IgM, however one patient had anti-HEV IgM. **Conclusion**: Superinfection with HAV in adult patient is uncommon in India. Prevalence of acute HEV infection in decompensated cirrhosis is low in the present study but presence of HEV superinfection in one patient corroborates the apprehension of liver function deterioration following superinfection with HEV virus.

**Keywords**: HEV; HAV; Superinfection; Liver cirrhosis

## INTRODUCTION

Hepatitis A virus (HAV) and Hepatitis E virus (HEV) are endemic in South Asia and are most common cause of acute hepatitis[1,2]. It is presumed that if a subject already has chronic liver disease additional infection by another hepatotropic virus like hepatitis A virus (HAV) and hepatitis E virus (HEV) would be poorly tolerated[3-5] But only limited studies have been done to evaluate the role of HAV and HEV superinfection in patients of CLD.

Since transmission routes of HEV and HAV are similar, correlation between the seroprevalence rates of both the viruses may be assumed. However it has been seen in various seroprevalence studies that HAV is responsible for acute hepatitis in childhood with the prevalence of HAV rising till 10-12 years of age then reaching a plateau and due to the presence of lifelong immunity following HAV infection repeat attacks are infrequent[6,7]. There is only little information on the perpetuation of HEV in nature and the exact seroprevalence of the virus in different geographical regions. In India the seroprevalence of

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HEV was found to be more evenly distributed over all age groups but rising somewhat after 30 years of age[6,7].

In December 1996 the advisory committee on Immunization practices (ACIP) recommended the immunization of all the patients with CLD against HAV infection[8]. India being endemic for HAV, the prevalence of pre-existing antibodies against HAV due to subclinical exposure in childhood may be high and therefore vaccination may not be needed.[9,10]

In endemic areas such as South Asia most adult patients already have been exposed to HAV but could still be susceptible to hepatitis E virus infection. Higher prevalence of HEV infection has been seen in HBV carriers[4]. Since natural HEV exposure does not bestow significant protection as observed in HAV infection, recurrent episodes of HEV infection in the same patient is possible[11,12]. Limited data available suggests that superinfection with HEV causes hepatic decompensation and increased morbidity and mortality[4,13-15]. However, only limited data is available on the prevalence of HAV and HEV infection among patients with chronic liver disease in India. The increasing proportion of susceptible population to enterically transmitted viral hepatitis has implications to future prevention and control programmes. Hence this study was undertaken to determine the prevalence of HAV and HEV superinfection in patients of CLD and their role in disease exacerbation.

## MATERIALS AND METHODS

The present study was a prospective study conducted in the Departments of Microbiology and Medicine, Maulana Azad Medical College & associated Lok Nayak & G. B. Pant hospitals in New Delhi during January 2003-March 2004. Over these 15 months 53 patients of Cirrhosis attending the Medical Outpatient Department or admitted in the Medical Wards of Lok Nayak Hospital were included in the study. The diagnosis of cirrhosis was based on the features of chronic liver disease associated with features of portal hypertension. Sonographic findings showing characteristic changes in the liver (shrunken liver with nodular surface), and features of portal hypertension (Porto-systemic shunts, ascites and splenomegaly), and upper GI endoscopy (showing esophageal, gastric varices) helped in corroborating the diagnosis. Liver biopsy could be performed in 31/53 cases. Biopsy could not be performed in 22 cases either due to non compliance of the patients or the deranged coagulation profile. Informed consent was taken from these patients before their inclusion in the study. The patients were evaluated on the basis of detailed history and physical examination. The patients in which there were apparent causes of decompensation either due to septicemia, hepatotoxic drugs, recent alcohol intake or those having hepatocellular carcinoma were excluded from the study. Detailed history for exposure to hepatotoxic drugs and recent alcohol consumption was obtained.

Blood culture sensitivity was put up for patients suspected of having sepsis. Spontaneous bacterial peritonitis was ruled out by doing direct microscopic examination and culture sensitivity of ascitic fluid.

Seven mL of blood was collected from all patients and it was subjected to a battery of biochemical and hematological investigations. Serum for viral serology was stored at −20℃ till further testing was done. Serological tests were performed using commercially available ELISA kits according to the manufacturer's instructions. The various serological tests performed in all the patients included- HBsAg provided by BIORAD, antibody to the core antigen (HBc IgG) using ELISA kits by Biochem Immunosystems, IgM anti-HAV provided by S. R. L. Medical Biological Service and IgM anti-HEV provided by ADALTIS. Validity of the test run was done and results were calculated as per the manufacturer's instructions provided with the kit. Serum sample giving borderline results were retested and those repeatedly giving borderline values were considered negative.

Statistical analysis: The information collected in the study was coded and transferred to a personal computer and analyzed using SPSS windows version 11. The Probability value (*P*-value) less than 0.05 were regarded as statistically significant.

## RESULTS

The present study included 53 cases of cirrhosis as a result of Hepatitis B virus . The mean age ± standard deviation of the study group was 46.81 ± 13.26 yrs. Males predominated in the study group with the Male:Female ratio of 2.7:1. The duration of current illness varied from 3 to 22 days (median: 13 days).

All the patients presented with severe hepatic dysfunction, as indicated by presence of features suggesting decompensation i. e. ascites, variceal bleeding, jaundice and hepatic encephalopathy in varying combinations. Ascites was the most common presentation, seen in 79.24% , followed by jaundice in 75.47% of the patients Hemetemesis was present in 39.62 % of the patients and 47.16% of the patients presented with frank features of hepatic encephalopathy.

Serum bilirubin ranged from 0.8 mg/dL to 24 mg/dL (median 12.3 mg/dL). ALT levels ranged from 14 IU/L to 780 IU/L (median 232 IU/L). Serum albumin concentration varied from 1.2 to 4.2 gm% (median 2.8 gm %). Twenty eight patients had prothrombin time more than 3 sec beyond control value. Mortality in the study group was (15/53) 28.3% , the patient having HEV super infection also died.

All the 53 patients had evidence of HBV infection as anti HBc IgG could be detected in all these 53 patients. Hepatitis B surface antigen was present in 20 out of 53 cases of Cirrhosis. IgG anti HAV could be detected in ( 51/ 53) patients whereas IgM anti- HAV was not detected even in a single patient. The incidence of acute HEV infection was also less with IgM anti- HEV being present only in one patient. This patient was also positive for HBsAg . The patient having HEV superinfection presented with signs and symptoms of decompensation like ascites, jaundice and splenomegaly though other common features like hepatic encephalopathy or bleeding manifestations were absent.

## DISCUSSION

HAV superinfection can cause devastating injury in the presence of underlying chronic hepatocellular injury[5, 13]. The estimated case fatality rate due to HAV superinfection has been reported as 11.7% in patients with underlying diagnosis of chronic HBV infection and 4.6 % in patients with underlying CLD[5]. Various seroprevalence studies conducted have shown that in developing countries like India exposure to the virus is more or less universal in the early years of childhood[14,15]. In developing countries like India HAV is considered to be an infrequent cause of decompensation in cases of CLD[9, 10] but with improved sanitation measures the trends are changing and universal exposure is not the rule by early childhood. In the present study the prevalence of HAV infection as assessed on the basis of IgG anti - HAV antibody was present in almost 96 % cases but even in the other two patients´ acute infection as a result of HAV was absent. Our study population already have been exposed to the virus and have developed immunity and since none of the patients had IgM anti HAV it can be assumed that routine vaccination for HAV is not recommended for endemic countries like India.

Several questions regarding the pathogenesis of liver injury and its natural history remains unanswered even two decades after the discovery of Hepatitis E virus. In endemic areas like India most adults though already exposed to HAV, remain susceptible to HEV infection. Because of the similarities of two viruses HEV could also be expected to cause severe illness in patients with underlying CLD. Though not much information is available on HEV superinfection , few studies have documented more severe outcome with the occurrence of decompensation in patients of CLD as a result of HEV superinfection[4,13,16,17].

In the present study only one case of HEV superinfection (1.8 %) could be detected in patients of decompensated cirrhosis which is different from the other available data from India (Lucknow)[17]. The later study had shown a very high incidence of HEV superinfection i. e. 44% in decompensated cases of liver cirrhosis. There is another seroprevalence study from India (Vellore) that showed 3.4% prevalence of acute HEV infection in CLD patients[16].

It seems probable that the HEV prevalence varies in different geographical regions , a conclusion,

supported albeit indirectly, by various seroprevalence studies showing different prevalence of HEV in different geographical regions. Further studies are needed however to validate the exact incidence of HEV superinfection in CLD patients and the need for developing an HEV vaccine.

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