Superimposed acute hepatitis E infection in patients with chronic liver disease

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Background: The natural history of infection with hepatitis E virus (HEV) in patients with chronic liver disease (CLD) is not well described. Our study aims to document the presentation, course and outcome of HEV superinfection in patients with CLD. Methods: Over an 18-month period, ten patients with CLD were diagnosed to have HEV superinfection by detection of anti-HEV IgM antibodies in a setting of acute worsening. These patients were tested for HBsAg, IgM anti-HBc, anti-hepatitis C virus antibodies and IgM anti-hepatitis A virus antibodies, and were followed-up. Results: The etiology of underlying CLD in the 10 patients (9 men; mean [SD] age 42.4 [10.3] years) was alcohol in five patients, hepatitis B in two, hepatitis C in one and cryptogenic in two. Seven patients presented for the first time with recent-onset liver decompensation (median duration 27 days, range 7-45). All 10 had ascites and 7 had hepatic encephalopathy. Four patients developed renal failure during the course of illness. The median (range) bilirubin, ALT and albumin levels at presentation were 18.6 (4.9-32.6) mg/dL, 105 (28-6610) IU/L and 32 (29-41) g/L, respectively. At 8 weeks, only one patient had normalization of serum bilirubin or ALT levels. Three patients (30%) died, including two of renal failure and one of massive upper GI bleed. Conclusions: Superinfection with HEV in patients with CLD causes severe liver decompensation, which is frequently complicated with hepatic encephalopathy and renal failure. Acute hepatitis E in these patients has a protracted course with high morbidity and mortality. [Indian J Gastroenterol 2004;23:50-52]

Key words: Hepatitis E virus, superinfection

Hepatitis E virus (HEV) infection is generally a self-limiting illness that carries low mortality.1 2 HEV has been implicated in most epidemics and sporadic cases of viral hepatitis in endemic areas.3 4 HEV infection during pregnancy affects the maternal and fetal outcome adversely and is associated with a high case-fatality rate.5

The prevalence of IgG anti-HEV antibodies among the adult population in endemic regions is only 33%-40%.6 More than 80% of chronic liver disease (CLD) patients lack these antibodies.7 This may predispose them to severe liver decompensation with superimposed HEV infection, similar to that documented previously with hepatitis A virus (HAV) superinfection.8 9 We report 10 patients with CLD of varying etiology, who presented with HEV superinfection to one unit of our tertiary-level referral hospital. This report aims to document the presentation, course and outcome of HEV superinfection in patients with CLD.

Methods

All patients admitted to one Gastroenterology unit at our hospital, with the diagnosis of CLD and recent worsening of hepatic function, were screened for the presence of HEV superinfection. Sudden worsening was defined arbitrarily as 'recent (within the last 3 months) appearance of jaundice or ascites'. CLD was diagnosed based on clinical, biochemical, ultrasonographic and endoscopic findings. HEV superinfection was diagnosed by the presence of IgM anti-HEV antibodies, which were detected using an enzyme immunoassay (GDSrl, Milan, Italy). This assay uses synthetic target HEV peptides corresponding to ORF2 and ORF3 structural proteins. Samples with optical density above the cut-off (mean of negative controls + 0.200) were considered reactive.

Patients with HEV superinfection were also tested for HBsAg, IgM anti-HBc, anti-hepatitis C virus antibodies and IgM anti-HAV antibodies (Biokit SA, Barcelona, Spain), and were screened for other causes of worsening in hepatic function including spontaneous bacterial peritonitis and variceal bleed. Detailed history for exposure to hepatotoxic drugs and recent alcohol consumption was obtained. Patients with evidence of hepatocellular carcinoma on ultrasound or computed tomogram, or presence of other forms of acute viral hepatitis (detectable IgM anti-HAV or IgM anti-HBc) were excluded. The patients were followed up for assessment of liver function, renal parameters and survival outcome.

Results

Over an 18-month period, 10 patients (9 men; mean [SD] age 43 [10.6] years) with acute worsening and CLD were diagnosed to have HEV superinfection. The underlying etiology of CLD was alcohol in 5 patients, hepatitis B virus (HBV) in 2 patients, hepatitis C virus (HCV) in one patient, and cryptogenic in 2 patients. Seven of these 10 patients presented for the first time with recent-onset hepatic decompensation. Median duration of worsening

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was 27 days (range 3-45). A definite prodrome in the form of low-grade fever, fatigue, nausea was observed in 6 patients; 3 patients had pruritus in addition. The commonest feature of hepatic decompensation at presentation was ascites (10/10) followed by hepatic encephalopathy (7/10). Four patients developed renal failure during the course of illness. None of the patients had evidence of acute co-infection with HAV or HBV.

Median serum bilirubin level at the time of presentation was 18.6 mg/dL (range 4.9-32.6); it peaked during the first and second weeks of the illness and started falling thereafter, though only one patient had normal levels at 8-week follow-up (Table). Median ALT and albumin levels at presentation were 105 IU/L (range 28-6610) and 3.2 g/dL (2.9-4.1), respectively; these continued to be abnormal at 8-week follow-up in some patients (Table). Prothrombin time remained deranged in all patients throughout the course of illness.

Ascites improved with dietary modification and diuretics in 5 patients but remained difficult to manage in 2 patients even at the end of the follow-up period. Hepatic encephalopathy responded to anti-coma regimen in 4 of 7 patients, whereas one patient has recurrent HE requiring frequent admissions. Renal failure improved in 2 of 4 patients. Three patients (30%) died after a mean duration of 2 months; two deaths were related to renal failure and one to massive variceal bleed.

Discussion

HEV infection has classically been described as causing an acute and self-limiting illness. Several questions regarding the pathogenesis of liver injury and its natural history remain unanswered two decades after the discovery of this virus. HEV infection is endemic in South Asia, and is the most common cause of acute hepatitis in this region. The prevalence of IgG anti-HEV antibodies among healthy blood donors in South Asia is around 18%. Similar figures have been reported in patients with underlying CLD. 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.

Patients in our study presented with severe hepatic dysfunction, as indicated by the presence of ascites in all and hepatic encephalopathy in most patients. Most of our patients (7/10) reported for the first time with superimposed HEV infection, which had in all probability upset the delicate balance of hepatic reserve. Renal failure in the absence of underlying parenchymal renal disease was a common feature and contributed to death in two patients. Hamid et al reported 4 patients with CLD and HEV superinfection; one patient in their series died following renal failure and spontaneous bacterial peritonitis. Only one of our patients had achieved normal serum bilirubin and transaminases levels at the end of the follow-up period (2.1.5 months); in contrast, liver function recovers within 6 weeks in most adults with hepatitis E without underlying CLD.

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. In fact, this observation has prompted recommendation of hepatitis A vaccine for patients with CLD. Our study emphasizes that HEV shares this propensity of causing severe disease in patients with CLD.

Ours is a preliminary study describing the presentation, course and outcome of HEV superinfection in patients with CLD, and has certain limitations. Further studies are needed to assess the prevalence of IgM anti-HEV in patients with CLD with and without recent worsening, and factors governing the outcome in these patients.

To summarize, superinfection with HEV in patients with underlying CLD causes severe liver decompensation that is frequently complicated with hepatic encephalopathy and renal failure. Hepatitis E infection in this setting has a protracted course with high morbidity and mortality. With the future availability of an effective HEV vaccine, patients with CLD may be among the group of prime beneficiaries, along with pregnant women and travelers.

References

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