Not So (A) Cute: Chronic Evolution of Hepatitis E Virus

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ABSTRACT

Although HEV causes self-limiting acute infection, an atypical clinical presentation with persistent viremia in immunocompromised individuals has emerged recently, in developed countries. In the absence of travel to endemic regions, indigenous HEV infection due to zoonotic viral strains are implicated in such chronic cases. Presently, IFN-α-2a and Ribavirin are proving effective in treating chronic hepatitis E patients. The underlying mechanisms of this chronic adaptation is poorly understood so far and therefore, a comprehensive clinical, virological and molecular study is needed to control the disease.

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Key words: HEV; Chronic infection; Immunocompromised; Zoonosis


INTRODUCTION

Among the human hepatitis viruses (A, B, C, D and E), only HBV, HCV and HDV are known to cause chronic infections. Generally, HEV infection is manifested by a self-limiting acute hepatitis that may be symptomatic or asymptomatic with an overall fatality rate of about 2%[1]. However, in developing countries, cases of mortalities due to fulminant liver failure may also occur in about 20% of pregnant women or in persons with pre-existing chronic liver disease[2]. In contrast, in industrialized countries like USA, Japan and many European nations, acute hepatitis E occurs sporadically. Although HEV infection does not develop into chronicity in immunocompetent individuals, viremia can persist for long in immunocompromised patients[3]. Historically, a retrospective analysis of Japanese T-cell lymphoma patients with unresolved hepatitis, had provided the first indication of possible chronic hepatitis E[3]. In the recent years, several cases of persistent HEV-infection associated with progressive liver disease in industrialized countries have been reported in German[4], French[5] and Dutch[6] immunosuppressed patients. Of the four known genotypes of HEV, genotypes 1 and 2 infect only humans and non-human primates whereas genotypes 3 and 4 are zoonotic and infect swine and some other mammals in addition to humans. Although genotypes 3 and 4 appear less pathogenic compared to 1 and 2, these strains have been implicated in the European chronic cases. However, there is no report available on specific viral mutations or genetic variants related to this chronic shift. A very recent, incredible work of Kamar and colleagues has described chronic HEV infection in more than 60% of solid organ transplant recipients[6]. Cases of viral reactivation after stem cell transplantation were, also, reported three years back[7]. HEV related liver cirrhosis is not known so far but very interestingly, development of cirrhosis in a liver transplant recipient with chronic HEV infection was reported, too[7].

Therapy with immunosuppressive drugs, like Tacrolimus (FK-506 or Fujimycin) is considered as the main predictive factor for the development of chronic hepatitis E in infected individuals[8]. However, the mechanisms behind establishing chronic infection and its consequences are hitherto not known. A lower CD4+ T cell count has been observed in patients in whom chronic hepatitis E evolved compared to those who self-cleared the virus[9]. Hence, the establishment of chronic HEV infection due to impaired adaptive immune responses under immunosuppression in the clinical situations may be a potential reason. Pegylated interferon-α-2a (pegIFN-α-2a) and Ribavirin are the most widely used drugs to treat chronic viral hepatitis. Needless to say, there has been no established treatment for HEV infection. But in the current era of chronic evolution, pegIFN-α-2a has been successfully used for treating HEV chronic infection in transplant patients[10]. Further, Ribavirin is also shown to inhibit the viral replication and induce a sustained virological response in patients with chronic HEV infection[11]. Therefore, the recent trend of HEV chronic infection (Figure 1) and...
its impact on severe liver disease at least in the immunocompromised individuals, certainly makes hepatitis E very important. A comprehensive clinical, virological and molecular data are needed in follow-up studies to understand and control this viral paradigm shift.

**Figure 1** The hepatitis viruses and the evolution of HEV from acute to chronic infection.

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