

## Evolving Manifestations of Hepatitis E Virus: Aren't We Overinterpreting?

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### ABSTRACT

HEV continues to emerge as a potential human pathogen with novel manifestations, like chronic hepatitis as well as neuropathy and arthralgia. Here, we briefly discuss two recently published reports: the first of an immunocompetent-chronic hepatitis E patient, and the second of an acute hepatitis E patient with rash and arthralgia. The first reported patient had a history of decades-long immunosuppressive therapy for an autoimmune disease that was further continued after the onset of hepatitis E. In the second case, although the hepatitis E patient had serological evidences of past herpes infections, the authors overlooked the fortuitous or indirect association of herpes-related rash and arthralgia. Therefore, such hepatitis E cases need to be a very carefully reported without overstating or overinterpreting the clinical observations.

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**Key words:** HEV; Chronic hepatitis E; Neuropathy; Arthralgia

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### EDITORIAL

Hepatitis E virus (HEV) is inherently a hepatotropic virus that generally manifests by a self-limiting acute infection. HEV has however, recently evolved to cause chronic liver infections<sup>[1]</sup> as well as neurologic signs and symptoms<sup>[2]</sup>. Hepatitis E infection may be symptomatic or asymptomatic with an overall fatality rate of about 2% worldwide<sup>[3]</sup>. Of the four recognized genotypes of human HEV, zoonosis of genotypes-3 and -4 have been implicated in the European and North American cases of acute and chronic hepatitis E<sup>[1]</sup>. Immunosuppressive drugs are considered as the cause of chronic hepatitis E which might result in suboptimal or impaired HEV-specific host immune responses, favoring viral persistence<sup>[4]</sup>. Nevertheless, the molecular mechanisms of HEV-associated neuropathy in immunocompetent individuals or persistent HEV infection in immunocompromised patients have hitherto not been clearly understood.

Chronic hepatitis E has been only observed in clinically immunosuppressed individuals, such as solid-organ, stem-cell and bone-marrow transplant recipients, leukemia patients, and HIV co-infection patients, so far<sup>[1,4]</sup>. Interestingly, in a recent report, Grewal et al. had described chronic infection of HEV genotype-3 in an immunocompetent patient with systemic lupus erythematosus<sup>[5]</sup>. The patient had a history of an autoimmune disease who was treated with immunosuppressants, like hydroxychloroquine and steroids for about 40 years before the onset of hepatitis E. Upon presenting elevated liver-enzymes levels, the patient was further given azathioprine and steroids for 7 months. In the following 2 years, having persisting elevations in liver-enzymes with progressive liver fibrosis, the patient had to continue the two drugs. In this report, the authors however, did not mention the duration of this extended course of immunosuppressive therapy. Further, it would have been more appropriate if the authors had provided immunologic profiles, like total lymphocyte count, CD4+, CD8+, and CD3+ T cell counts, including anti-HEV specific T-3 cell response to conclude their findings.

It is unclear how HEV reaches the liver, and therefore, extrahepatic site(s) of replication would be very possible. Post-infection rashes,

arthralgias or Adult-Onset Still's Disease (AOSD) are known to be triggered by many herpes viruses, adenoviruses, enteroviruses, retroviruses, paramyxoviruses, rubella virus and hepatitis viruses A, B and C (HAV, HBV and HCV)<sup>[2]</sup>. A previous report on association of acute polyarthritis with hepatitis E has shown evidence for past immunization against herpes viruses, like cytomegalovirus (CMV) and Epstein-Barr virus (EBV)<sup>[6]</sup>. In another interesting case, Al-Shukri et al. has recently reported an acute hepatitis E patient with rash and arthralgia<sup>[7]</sup>. Notably, the patient's serology test has revealed markers of past infections with CMV and EBV. In this case, the authors have neither mentioned the age of herpes infection nor the history of high fever, rash, arthralgia or AOSD-like symptoms, if any. Nevertheless, the time-related occurring and simultaneous recovery of the hepatitis E and arthralgia does indicate a unique manifestation of HEV. However, a fortuitous or indirect association of rash and arthralgia with post-herpes infection in the patient could not be ruled out. Although, the underlying mechanisms are poorly understood, synergistic interaction of cell-mediated and humoral immune responses are suggested. For CMV, immune-pathogenic link with the elevated levels of pro-inflammatory cytokines, like interleukins (IL-1, IL-6 and IL-18), interferon (IFN  $\gamma$ ), tumor necrosis factor (TNF) and macrophage colony-stimulating factor (M-CSF), including activation of macrophages, NK cells and B-lymphocytes has been proposed<sup>[8]</sup>. It might be very possible that the clinically silent or asymptomatic illness that was actually initiated by CMV or EBV in the past was reactivated by HEV in the present case.

In sum, HEV is evolving as a potential human pathogen, noticed by its novel manifestations. In clinical cases, it would be more appropriate to look into patient's history and specific immunologic markers while establishing chronic hepatitis E in immunocompetent individuals or a direct role of HEV infection in neuropathy and arthralgia. Therefore, a very cautious note has to be taken on

reporting such cases without overstating or overinterpreting the clinical data.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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