HHS Public Access

Author manuscript

Liver Int. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Liver Int. 2016 April ; 36(4): 477–479. doi:10.1111/liv.13085.

Causation by HEV of extrahepatic manifestations remains unproven

Zongdi Feng[1,2]

[1]Center for Vaccines and Immunity, The Research Institute at Nationwide Children's Hospital, Columbus, OH 43205

[2]Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH 43205 USA

HEV is a common cause of acute viral hepatitis worldwide but new data suggest that HEV infection is associated with a spectrum of extrahepatic manifestations (EMs). In some cases, the incidence rates were significantly higher than those in general population. This result raises the possibility that HEV replication outside the liver causes neurological and other symptoms described in the accompanying review by Kamar et al.

A brief review of the HEV life cycle is helpful for understanding its related pathology. HEV is usually transmitted enterically. Through a yet poorly understood mechanism, HEV penetrates the gut and enters the blood through which the virus reaches the liver to initiate its replication. Newly synthesized virions are released at both the basolateral and apical membranes of the infected hepatocytes. Virions released at the basolateral membrane return to the blood circulation and mediate subsequent rounds of infection, while those released at the apical membrane enter the biliary tract and are ultimately shed in feces. Replication of HEV is noncytopathic and the pathology is believed to be immune-mediated (1).

EMs associated with HEV infection may be caused by either direct or indirect mechanisms. Direct mechanisms involve replication of HEV in affected tissues as being the cause for the local tissue damage, whereas indirect mechanisms are caused by crossreactive immune responses post or during infection, by formation of immune complexes, or by secondary infection. As will be discussed below, compelling evidence for replication of HEV outside the liver is still lacking. However, crossreactive immune responses remain a possibility, at least for certain clinical symptoms.

Direct mechanisms

The potential for HEV entry and replication in cells other than hepatocytes cannot be dismissed. A broad host cell range may be facilitated by cloaking of HEV in host cell membrane (2, 3) and insertion of human sequences into the HEV genome (4-6). Membrane

Mailing address:

WA4013 Research Building 2, Center for Vaccines and Immunity, The Research Institute at Nationwide Children's Hospital, Columbus, OH 43205 USA, Tel: 614-355-2784; Fax: 919-722-3680, zongdi.feng@nationwidechildrens.org

Conflict of interest: None.

cloaking may result in nonspecific binding and uptake by different cell types (7). In addition, similarities between the membrane-encased HEV virion (eHEV) and exosomes (small vesicles involved in intercellular communication) raise the possibility that eHEV may penetrate immunologically privileged sites such as the central nerve system (CNS) as do exosomes (8, 9). Incorporation of host sequences into the hypervariable region of the HEV genome has been described in patients with persistent HEV infection (4, 5). In vitro data showed that these insertions provided growth advantages to the virus in culture and may also lead to altered cell tropism and host range (4, 6). However, no data indicate that these human sequence insertions resulted in HEV replication in extrahepatic tissues.

Compelling evidence supporting extrahepatic replication of HEV is generally lacking. Although the gut stands as the first physical barrier for the virus, there are no published data indicating that HEV replicates in human gut. Bose et al. detected replicating HEV in human placenta by negative-strand-specific RT-PCR and in situ hybridization (10). However, the titer of HEV was extremely low and barely above the detection limit. And only a few, if any, positive cells were detected by immunohistochemistry using an anti-pORF3 antibody. The viral loads in placenta also had no correlation with pregnancy outcome or the mortality of either the mothers or the babies (10). A more recent study described the detection of HEV-Ag in kidneys and infectious virus in urine from persons with HEV infection or monkeys with experimental acute HEV infection (11). However, replication of HEV in the kidney was not demonstrated. HEV RNA has also been detected in the cerebrospinal fluids (CSF) of hepatitis E patients (12). Interestingly, the viral sequences differed from those circulating in the blood, suggesting independent virus replication with the CNS (13). However, these sequence data need be interpreted with caution since different quasispecies do not necessarily represent independent replication, but could also be due to other reasons such as selection of particular viral populations by physical barriers between different compartments as well as antiviral immunity. Deep sequencing may be needed to assess the diversity of virus populations in different compartments to investigate if unique sequences were present in the CNS.

In summary, most published studies lack compelling evidence for active HEV replication in affected tissues and organs, making it unlikely that replication of HEV is directly responsible for these EMs. Even when low level replication is present, virus titer is another important factor to consider. More definitive molecular evidence for virus replication (presence of negative strand viral RNA) and their spatial-temporal correlation with pathological findings should be sought in the future to define the causal relationship between HEV and EMs.

Indirect mechanisms

Indirect mechanisms include crossreactive immune responses, generation of immune complexes, and secondary microbial infections. Most EMs associated with HEV infection are related to neurological problems and kidney injury (12). Whereas neurological problems usually occur post-infection and are likely caused by crossreactive immune responses, the kidney injury often involves deposition of immune complexes formed between viral

antigens and antibodies. In these scenarios, viral replication in affected tissues may not be necessary.

Under certain circumstances, immune responses directed against invading microbes crossreact with host antigens resulting in autoimmunity. This can be mediated by either crossreactive antibodies or T cells. As an example for crossreactivity, certain individuals with 2009 H1N1 influenza A infection or Pandemrix vaccine developed antibodies against the viral nucleoprotein that crossreact with the hypocretin receptor 2, resulting in sleep disorder narcolepsy (14). Crossreactive cytotoxic T cells have been described in patients with chronic hepatitis C (15). While neurological problems associated with HEV infection usually occur post-infection, which is suggestive of crossreactive immune responses as being involved, no data currently exist with regard to the generation of crossreactive antibodies or T cells during HEV infection.

Immune complexes formed between HEV antigens and antibodies may also contribute to EMs associated with HEV infection. Deposition in the glomerulus of immune complexes may result in tissue damage involving kidney, skin and the vascular system. However, since membrane-cloaked HEV predominates in the blood and coexists with HEV-specific antibodies (2), it seems unlikely that formation of immune complex is responsible for HEV-associated EMs.

Finally, HEV infection may trigger the reactivation of latent viruses or co-infection by other microbes in certain individuals, particularly those who are immunocompromised. This could result in clinical symptoms depending on the tissues/organs that are affected by these secondary infections. The advancement of modern diagnostic tools and a better understanding of the etiology of diseases hold promise for identifying mechanisms for EMs associated with HEV infection, and perhaps with other hepatitis viruses.

In summary, there is precedent for direct and indirect tissue damage by viruses. For HEV, this remains largely speculative in the absence of data documenting extrahepatic replication of the virus or induction of crossreactive antibody or T cell responses. This is an important future direction for research on this understudied virus.

Acknowledgements

the author would like to thank Christopher Walker, Mark Peeples, and Jonathan Honegger for helpful discussion and reading of the manuscript.

Financial support: This work was supported by the Pinnacle Research Award in Liver Diseases from the American Association for the Study of Liver Diseases Foundation, the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (R21AI122228) and the internal startup funds from the Nationwide Children's Hospital (Z.F.).

List of abbreviations

HEV	Hepatitis E virus
EM	extrahepatic manifestations

CNS	central nervous system
CSF	cerebrospinal fluids

References

1. EMERSON SU, PURCELL RH. Hepatitis E virus. Rev Med Virol. 2003; 13(3):145–54. [PubMed: 12740830]
2. TAKAHASHI M, TANAKA T, TAKAHASHI H, HOSHINO Y, NAGASHIMA S, JIRINTAI, et al. Hepatitis E Virus (HEV) strains in serum samples can replicate efficiently in cultured cells despite the coexistence of HEV antibodies: characterization of HEV virions in blood circulation. J Clin Microbiol. 2010; 48(4):1112–25. [PubMed: 20107086]
3. NAGASHIMA S, JIRINTAI S, TAKAHASHI M, KOBAYASHI T, TANGGIS, NISHIZAWA T, et al. Hepatitis E virus egress depends on the exosomal pathway, with secretory exosomes derived from multivesicular bodies. Journal of General Virology. 2014; 95(10):2166–75. [PubMed: 24970738]
4. SHUKLA P, NGUYEN HT, TORIAN U, ENGLE RE, FAULK K, DALTON HR, et al. Cross-species infections of cultured cells by hepatitis E virus and discovery of an infectious virus-host recombinant. Proc Natl Acad Sci U S A. 2011; 108(6):2438–43. [PubMed: 21262830]
5. LHOMME S, ABRAVANEL F, DUBOIS M, SANDRES-SAUNE K, MANSUY J-M, ROSTAING L, et al. Characterization of the Polyproline Region of the Hepatitis E Virus in Immunocompromised Patients. Journal of Virology. 2014; 88(20):12017–25. [PubMed: 25100839]
6. SHUKLA P, NGUYEN HT, FAULK K, MATHER K, TORIAN U, ENGLE RE, et al. Adaptation of a Genotype 3 Hepatitis E Virus to Efficient Growth in Cell Culture Depends on an Inserted Human Gene Segment Acquired by Recombination. Journal of Virology. 2012; 86(10):5697–707. [PubMed: 22398290]
7. FENG Z, LEMON SM. Peek-a-boo: membrane hijacking and the pathogenesis of viral hepatitis. Trends in Microbiology. 2013
8. EL ANDALOUSSI S, LAKHAL S, MÄGER I, WOOD MJA. Exosomes for targeted siRNA delivery across biological barriers. Advanced Drug Delivery Reviews. 2013; 65(3):391–97. [PubMed: 22921840]
9. ZHUANG X, XIANG X, GRIZZLE W, SUN D, ZHANG S, AXTELL RC, et al. Treatment of Brain Inflammatory Diseases by Delivering Exosome Encapsulated Anti-inflammatory Drugs From the Nasal Region to the Brain. Mol Ther. 2011; 19(10):1769–79. [PubMed: 21915101]
10. BOSE PD, DAS BC, HAZAM RK, KUMAR A, MEDHI S, KAR P. Evidence of extrahepatic replication of hepatitis E virus in human placenta. Journal of General Virology. 2014; 95(6):1266–71. [PubMed: 24622580]
11. GENG Y, ZHAO C, HUANG W, HARRISON TJ, ZHANG H, GENG K, et al. Detection and assessment of infectivity of hepatitis E virus in urine. J Hepatol. 64(1):37–43. [PubMed: 26362822]
12. DALTON HR, KAMAR N, VAN EIJK JJJ, MCLEAN BN, CINTAS P, BENDALL RP, et al. Hepatitis E virus and neurological injury. Nat Rev Neurol. 2015 advance online publication.
13. KAMAR N, IZOPET J, CINTAS P, GARROUSTE C, URO-COSTE E, COINTAULT O, et al. Hepatitis E Virus-Induced Neurological Symptoms in a Kidney-Transplant Patient with Chronic Hepatitis. American Journal of Transplantation. 2010; 10(5):1321–24. [PubMed: 20346067]
14. AHMED SS, VOLKMUTH W, DUCA J, CORTI L, PALLAORO M, PEZZICOLI A, et al. Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2. Science Translational Medicine. 2015; 7(294):294ra105–294ra105.
15. KAMMER AR, VAN DER BURG SH, GRABSCHEID B, HUNZIKER IP, KWAPPENBERG KMC, REICHEN J, et al. Molecular Mimicry of Human Cytochrome P450 by Hepatitis C Virus at the Level of Cytotoxic T Cell Recognition. J Exp Med. 1999; 190(2):169–76. [PubMed: 10432280]