The Hepatopathogenesis of Hepatitis E Virus Genotype 3

Mohammad Khalid Parvez

ABSTRACT

Of the zoonotic genotypes of hepatitis E virus, the genotype 3 (HEV3) has emerged as the most pathogenic strain causing chronic hepatitis in immunosuppressed patients in industrialized nations. The epidemiology of HEV3 is rather complex because of its hitherto well recognized sources and routes of transmission. Currently, ribavirin is the only effective drug that, however, induces mutations in viral polymerase gene leading to drug-resistance or -nonresponse, and teratogenic effects in pregnant women.

Key words: Hepatitis E virus; HEV3; Chronic hepatitis E; Zoonosis; Foodborne hepatitis E

© 2019 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.
HEV3 GENETIC VARIANTS

According to the latest classification, 10 designated subtypes of HEV (HEV3a-HEV3j) and 7 unassigned subtypes are proposed(28,29). Increased virulence associated with HEV3i, HEV3j and HEV3o strains are reported from patients with severe hepatitis in Japan(30). Complete sequencing of HEV3 RNA from acute, fulminant, and chronic patients as well as farmed pigs and wild boar have revealed genetic diversity suggesting its cross-species or host adaptations(27-29).

HEV3 AND PREGNANCY

Pregnant women with acute hepatitis E are at higher risk of morbidity and death than those with chronic hepatitis. Hepatitis E in pregnancy can take a fulminant course, resulting in fulminant hepatic failure, membrane rupture, spontaneous abortions, and stillbirths. Compared to HEV1, there are very few reported cases of HEV3 infection during pregnancy in industrialized countries(20-22). Very recently, cases of HEV3 infections acquired during pregnancy in immunocompetent French women who neither travelled abroad nor consumed raw or undercooked pork are reported(24). Though persistence of HEV has not been reported among patients treated with infliximab or azathioprine, it is observed in a patient receiving azathioprine and oral steroids(25). In another case report of a pregnant woman with chronic hepatitis E who received infliximab and azathioprine without adverse event, spontaneously resolved after delivery(26).

CURRENT TREATMENT AND LIMITATIONS

There is an effective HEV vaccine (HEV239 or Hecolin) available in China that is however, still inaccessible to other countries, including the USA and Europe(27). Ribavirin (RBV) is the only effective treatment of choice in HEV3 infected patients. Although, RBV clears the virus and induces a sustained virological response, emergence of HEV polymerase gene mutants (eg. G1634R/K) lead to drug-resistance or nonresponse to therapy(28,29). Further therapeutic limits of RBV include its teratogenic effects in pregnant women, potential to cause hemolytic anemia, dyspnea, insomnia and irritability(30).

CONCLUSION AND FUTURE PERSPECTIVES

HEV3 has recently evolved as the most pathogenic anthropozoonotic strain causing chronic hepatitis in immunosuppressed population in industrialized nations. Owing to limits of antiviral drugs, prevention of HEV3 relies primarily on avoiding undercooked pork and other products. Pregnant women with liver symptoms should be immediately hospitalized and diagnosed for HEV. In cases of acute liver failure, urgent liver transplant can be a lifesaving option.

REFERENCES

1. Smith DB, Simmonds P, members of the International Committee on the Taxonomy of Viruses Hepaviridae Study Group, Jameel S, Emerson SU, Harrison TJ, Meng XJ, Okamoto H, Van der Poel WH, Purdy MA. Consensus proposals for classification of the family Hepeviridae. J. Gen. Virol. 2015; 96:1191-1192. [PMID: 26015322]; [DOI: 10.1099/vir.0.001115]
2. Purcell RH, Emerson SU. Hepatitis E: an emerging awareness of an old disease. J. Hepatol. 2008; 48:494-503. [PMID: 18192058]; [DOI: 10.1016/j.jhep.2007.12.008]
3. Navaneethan U, Al Mohajer M, Shata MT. Hepatitis E and pregnancy: understanding the pathogenesis. Liver Int. 2008; 28:1190-1199. [PMID: 18662274]; [DOI: 10.1111/j.1478-3231.2008.01840.x]
4. Tam AW, Smith MM, Guerra ME, Huang CC, Bradley DW, Fry KE, Reyes GR. Hepatitis E virus (HEV): molecular cloning and sequencing of the full-length viral genome. Virology 1991; 185:120-131. [PMID: 1926770]
5. Nicot F, Jeanne N, Roulet A, Lefebvre C, Carcenac R, Manno M, Dubois M, Kamar N, Lhomme S, Abravanel F, Izopet J. Diversity of hepatitis E virus genotype 3. Rev. Med. Virol. 2018; 28:e1987. [PMID: 29939461]; [DOI: 10.1002/rmv.1987]
6. Meng, XJ. Zoonotic and foodborne transmission of hepatitis E virus. Semin. Liver Dis. 2013; 33:41-49. [PMID: 23564388]; [DOI: 10.1055/s-0033-1338113]
7. Parvez, MK. Chronic hepatitis E infection: risks and controls. Intervirology 2013; 56:213-216. [PMID: 23689166]; [DOI: 10.1159/000349888]
8. Dalton HR, Izopet J. Transmission and Epidemiology of Hepatitis E Virus Genotype 3 and 4 Infections. Cold Spring Harb. Perspect. Med. 2018; a032144. [PMID: 29154369]; [DOI: 10.1083/ndpd.2017.86]
9. Mansuy JM, Gallian P, Dimeligio C, Saune K, Arnaud C, Pelletier B, Morel P, Legrand D, Tiberghien P, Izopet J. A nationwide survey of hepatitis E virus. Hepatology 2016; 63:1145-1154. [PMID: 27082021]; [DOI: 10.1002/hep.28436]
10. Kamar N, Dalton HR, Abravanel F, Izopet J. Hepatitis E virus infection. Clin. Microbiol. Rev. 2014; 27:116-138. [PMID: 24396139]; [DOI: 10.1128/CMR.00057-13]
11. Dreier J, Juhl D. Autochthonous hepatitis E virus infections: a new transfusion-associated risk? Transit. Med. Hemotherapy: 2014; 41:29-39. [PMID: 24659945]; [DOI: 10.1159/000357098]
12. Satake M, Matsubayashi K, Hoshi Y et al. Unique clinical courses of transfusion-transmitted hepatitis E in patients with immunosuppression. Transfusion 2017; 57:280-288. [PMID: 28144952]; [DOI: 10.1111/trf.13994]
13. Suneetha PV, Pischke S, Schlaphoff V, Grabowski J, Fytiti P, Gronert A, Brenner B, Markova A, Jaroszewicz J, Bara C, Manns MP, Cornberg M, Wedemeyer H. Hepatitis E virus (HEV)-specific T-cell responses are associated with control of HEV infection. Hepatology 2012; 55:695-708. [PMID: 22066345]; [DOI: 10.1002/hep.24738]
14. Smith DB, Simmonds P, Izopet J, Oliveira-Filho EF, Ulrich G,
Parvez MK. HEV3 hepatopathogenesis

1. Johne R, Koenig M, Jameel S, Harrison TJ, Okamoto H, Van der Poel WH, Purdy MA. Proposed reference sequences for hepatitis E virus subtypes. *J. Gen. Virol.* 2016; 97:537-542. [PMID: 26743685]; [DOI: 10.1099/jgv.0.000393].

15. Wang B, Harms D, Papp CP, Niendorf S, Jacobson S, Lütgheetmann M, Pischke S, Wedemeyer H, Hofmann J, Bock CT. Comprehensive Molecular Approach for Characterization of Hepatitis E Virus Genotype 3 Variants. *J. Clin. Microbiol.* 2018; 56:e01686-17. [PMID: 29514938]; [DOI: 10.1128/JCM.01686-17].

16. Takahashi K, Okamoto H, Abe N, Kawakami M, Matsuda H, Mochida S, et al. Virulent strain of hepatitis E virus genotype 3, Japan. *Emerg. Infect. Dis.* 2009; 15:704-709. [PMID: 19402955]; [DOI: 10.3201/eid1505.081100].

17. Lu L, Li C, Hagedorn CH. Phylogenetic analysis of global hepatitis E virus sequences: genetic diversity, subtypes and zoonosis. *Rev. Med. Virol.* 2006; 16:5-36. [PMID: 16175650]; [DOI: 10.1002/rmv.482].

18. Lu Y, Qian HZ, Qin X, Jiang QW, Zheng YJ. Subtypes of genotype 3 hepatitis E virus in pigs. *Vet. J.* 2013; 197:509-511. [PMID: 23357066]; [DOI: 10.1016/j.tvjl.2012.12.023].

19. Vina-Rodriguez A, Schlosser J, Becher D, Kaden V, Groschup MH, Eiden M. Hepatitis E virus genotype 3 diversity: phylogenetic analysis and presence of subtype 3b in wild boar in Europe. *Viruses* 2015; 7:2704-2726. [PMID: 26008708]; [DOI: 10.3390/v7052704].

20. Andersson MI, Hughes J, Gordon FH, Ijaz S, Donati M. Of pigs and pregnancy. *Lancet.* 2008; 372:1192-1196. [PMID: 18926280]; [DOI: 10.1016/S0140-6736(08)61486-5].

21. Anty R, Ollier L, Péron JM, Nicand E, Cannavo I, Bongain A, et al. First case report of an acute genotype 3 hepatitis E infected pregnant woman living in South-Eastern France. *J. Clin. Virol.* 2012; 54:76-78. [PMID: 22336086]; [DOI: 10.1016/j.jcv.2012.01.016].

22. Tabatabai J, Wenzel JJ, Soboletzki M, Flux C, Navid MH, Schnitzler P. First case report of an acute hepatitis E subtype genotype 3c infection during pregnancy in Germany. *J. Clin. Virol.* 2014; 61:170-172. [PMID: 24996764]; [DOI: 10.1016/j.jcv.2014.06.008].

23. Mallet V, Le Mener S, Roque-Afonso A-M, Tsatsaris V, Manzer M-F. Chronic hepatitis E infection cured by pregnancy. *J. Clin. Virol.* 2013; 58:745-747. [PMID: 24140032]; [DOI: 10.1016/j.jcv.2013.09.023].

24. Bouthry E, Benachi A, Vivanti AJ, Letamendia E, Vauloup-Fellous C, Roque-Afonso AM. Autochthonous Hepatitis E during Pregnancy, France. *Emerg. Infect. Dis.* 2018; 24:1586-1587. [PMID: 30016249]; [DOI: 10.3201/eid2408.180105].

25. Grewal P, Kamili S, Motamed D. Chronic hepatitis E in an immunocompetent patient: a case report. *Hepatology* 2014; 59:347-348. [PMID: 23913727]; [DOI: 10.1002/hep.26636].

26. Charre C, Ramire C, Dumortier J, Abravanel F, Lhomme S, Gincul R, Scholtès C. Chronic Genotype 3 hepatitis E in pregnant woman receiving infliximab and azathioprine. *Emerg. Infect. Dis.* 2018; 24:941-943. [PMID: 29664396]; [DOI: 10.3201/eid2405.171845].

27. Parvez MK. Hepatitis E vaccine: time to let the cat out. *Gastroenterol. Hepatol. Res.* 2017; 6:2384-2385. [DOI: 10.17554/j.issn.2224-3992.2017.06.712].

28. Todt D, Gisa A, Radonic A, Nitsche A, Behrendt P, Saneetha PV, Pischke S, Bremer B, Brown RJ, Manns MP, Cornberg M, Bock CT, Steinmann E, Wedemeyer H. In vivo evidence for ribavirin-induced mutagenesis of the hepatitis E virus genome. *Gut* 2016; 65:1733-1743. [PMID: 27222534]; [DOI: 10.1136/gutjnl-2015-311000].

29. Parvez MK. The nonstructural polyprotein of Hepatitis E virus. *Future Microbiol.* 2017; 12:915-924. [PMID: 28686042]; [DOI: 10.2217/fmb-2017-0016].