

The Hepatopathogenesis of Hepatitis E Virus Genotype 3

Mohammad Khalid Parvez¹

¹ Department of Pharmacognosy, King Saud University College of Pharmacy, Riyadh 11451, Saudi Arabia.

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Mohammad Khalid Parvez, PhD, Associate Professor, Department of Pharmacognosy, King Saud University College of Pharmacy, P.O. Box 2457, Riyadh 11451, Saudi Arabia.

Email: khalid_parvez@yahoo.com

Telephone: +966-14675132

Fax: +966-14677245

Received: April 3, 2019

Revised: May 7, 2019

Accepted: May 10, 2019

Published online: June 21, 2019

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.

Parvez MK. The Hepatopathogenesis of Hepatitis E Virus Genotype 3. *Journal of Gastroenterology and Hepatology Research* 2019; **8(3)**: 2879-2881 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2575>

INTRODUCTION

Hepatitis E virus (HEV), the causative agent of hepatitis E belongs to genus *Orthohepevirus* of the virus family Hepeviridae^[1]. Globally, HEV infection accounts for an estimated mortality rate of ~2%, including 20-30% of pregnant women^[2,3]. The HEV genome is a single-strand positive-sense RNA (~7.2 kb) defined into a short 5' untranslated region (UTR), three open reading frames (ORF1, ORF2, and ORF3), a short 3' UTR, and a poly(A) tail^[4]. Of the hitherto identified seven genotypes (HEV1 to HEV7), HEV1, 2, 3, 4 and 7 are known to infect humans. The genotypes belong to a single serotype and are further subdivided into subtypes^[5]. Notably, while HEV1 and 2 are restricted to human (anthroposis), HEV3 and 4 infect both humans and swine as well other mammalian species (anthropozoonosis)^[6]. Modes of HEV transmission are mainly contaminated water and animal food, including vertical transmission and blood transfusion^[7] (Table 1). Unlike other genotypes, the epidemiology of HEV3 is rather complex because of its several sources and routes of transmission that vary from region to region and over time^[8].

HEV3 ANTHROPOZOONOSIS

Of the zoonotic genotypes of hepatitis E virus, HEV3 has emerged as the most pathogenic strain in industrialized nations^[6]. Pigs represent a large reservoir and potential source of HEV3 where human and swine HEV are genetically very close (~99%) in cases of direct transmission^[7]. In addition, the genetic detection of HEV3 in other mammalian species in Europe and the USA has supported its foodborne transmission due to the consumption of gourmet figatellu, offal, and game meat of wild boar or deer^[7] (Table 1). A recent epidemiological study has suggested the possibility of waterborne transmission of HEV3 in France^[9].

HEV3 CHRONICITY

Approximately 70% of HEV3 infections remain subclinical or self-limiting that may develop into fulminant hepatitis^[10] (Table 1). In the recent decade, autochthonous rather than travel-associated cases of HEV3 infections have been widely reported in industrialized coun-

Table1 Characteristic features of HEV3.

Geographical distribution	Reservoirs	Transmission	Gender/Age	Hepatic manifestations	Extrahepatic manifestations	High-risk population	Treatment
North-America, Europe, Japan	Swine, Wild boar	Foodborne, Animal products, Blood	Mostly males/ ≥40 years	Self-limiting acute hepatitis, Acute liver failure, Chronic hepatitis, Liver cirrhosis	Neuromuscular, Hematological, Renal	Immunosuppressed/Transplant recipients, Pre-existing liver conditions, Sewage workers, Swine herders, Zookeepers, Veterinarians	Ribavirin, IFN-alpha-2a

tries^[7,11]. Recently, HEV3 has emerged as the most pathogenic strain to cause chronic hepatitis and liver cirrhosis in immunosuppressed, transplant and transfusion patients in Europe, North America and Japan^[7,10,12] (Table 1). Chemotherapy with immunosuppressive drugs (eg. tacrolimus or FK-506) is considered as the main predictive factor for the development of chronicity where sub-optimal or impaired adaptive immune responses may be a potential reason^[13].

HEV3 GENETIC VARIANTS

According to the latest classification, 10 designated subtypes of HEV (HEV3a-HEV3j) and 7 unassigned subtypes are proposed^[14,15]. Increased virulence associated with HEV3i, HEV3j and HEV3o strains are reported from patients with severe hepatitis in Japan^[16]. 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^[17-19].

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^[20-23]. 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 anthrozoönotic 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 im-

mediately hospitalized and diagnosed for HEV. In cases of acute liver failure, urgent liver transplant can be a lifesaving option.

REFERENCES

- Smith DB, Simmonds P, members of the International Committee on the Taxonomy of Viruses Hepeviridae 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.0.000115].
- 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].
- 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].
- 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].
- 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].
- 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].
- Parvez, MK. Chronic hepatitis E infection: risks and controls. *Intervirology* 2013; **56**:213-216. [PMID: 23689166]; [DOI: 10.1159/000349888].
- 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: 10.1038/nrdp.2017.86].
- Mansuy JM, Gallian P, Dimeglio C, Saune K, Arnaud C, Pelletier B, Morel P, Legrand D, Tiberghien P, Izopet J. A nationwide survey of hepatitis E viral infection in French blood donors. *Hepatology* 2016; **63**:1145-1154. [PMID: 27008201]; [DOI: 10.1002/hep.28436].
- 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].
- Dreier J, Juhl D. Autochthonous hepatitis E virus infections: a new transfusion-associated risk? *Transfus. Med. Hemotherapy.* 2014; **41**:29-39. [PMID: 24659945]; [DOI: 10.1159/000357098].
- 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].
- Suneetha PV, Pischke S, Schlaphoff V, Grabowski J, Fytily P, Gronert A, Bremer 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: 22006345]; [DOI: 10.1002/hep.24738].
- Smith DB, Simmonds P, Izopet J, Oliveira-Filho EF, Ulrich RG,

- Johne R, Koenig M, Jameel S, Harrison TJ, Meng XJ, 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, Jacobsen S, Lütgehetmann M, Pischke S, Wedermeyer 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 subgenotype 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, Mamzer 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, Ramière 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, Suneetha 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].
 30. Pradat P, Virlogeux V, Gagnieu MC, Zoulim F, Bailly F. Ribavirin at the era of novel direct antiviral agents for the treatment of hepatitis C virus infection: relevance of pharmacological monitoring. *Adv Hepatol.* 2014; **2014**:493087. [DOI: 10.1155/2014/493087].