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Review Article

Hepatitis E Virus: A Silent but Emerging Threat

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Abstract

Hepatitis E outbreaks pose a significant threat to public health in developing countries. The mortality rate is generally around 2% but can be higher than 20% in pregnant women in India. The virus responsible for hepatitis E, known as HEV, has been found in several animal species, including swine. Genotypes 3 and 4 of HEV have been isolated from humans and animals and are known to be zoonotic pathogens. Seroprevalence studies in animals and humans suggest that HEV infections occur globally. Populations in developed countries are typically infected with HEV through the consumption of undercooked animal meats, while undeveloped countries are typically infected with HEV via contaminated water. In addition, there have also been reports of HEV transmission through blood transfusions and organ transplants. In this short review, we summarise the virology of hepatitis E, the epidemiology of hepatitis E, the prevalence of HEV infection in animals and humans, and the modes of zoonotic transmission of HEV.

Keywords: Hepatitis E; Hepatitis E virus; Swine; Zoonotic; Seroprevalence

Introduction

Hepatitis E is a viral form of hepatitis that is transmitted through the enterically. It is a significant public health concern in developing countries in Asia and Africa and industrialised countries such as the US and Europe. The mortality rate for hepatitis E is generally low but can be as high as 28% for pregnant women [1]. The virus responsible for the disease, known as hepatitis E virus (HEV), is primarily spread through contaminated water or food. In developed countries, cases of hepatitis E have been reported in travellers returning from areas where the disease is prevalent and in individuals with no known risk factors. In areas with poor sanitation, outbreaks of hepatitis E can occur through the contamination of drinking water [2]. The discovery of HEV in animal species such as swine and chickens has expanded our understanding of the virus and its ability to infect different hosts [3,4]. This has raised concerns about the possibility of zoonotic transmission of the viral disease.

Virology of hepatitis E virus

Hepatitis E is a viral illness caused by the Hepatitis E virus (HEV), which can be found in humans and various animal hosts, including swine [5]. The HEV belongs to the viral family known as *Hepeviridae*, which is divided into two genera: *Orthohepevirus* and *Piscihepevirus*. The *Orthohepevirus* genus contains four species: *Orthohepevirus* A-D. *Orthohepevirus* A includes several genotypes that can infect humans, including HEV-1, HEV-2, HEV-3, and HEV-4. HEV-3 and HEV-4 can also infect swine. Recently, additional genotypes, such as HEV-5 and HEV-6 in wild boars and HEV-7 in camels, have been identified and are believed to belong to *Orthohepevirus* A. The HEV has a single-stranded RNA genome with a cap at its 5' end and a poly-A tail at its 3' end. The genome contains three open reading frames (ORFs) that encode non-structural proteins, such as an RNA-dependent RNA polymerase

and a capsid protein [6]. Humans typically become infected with HEV through the oral route and shed the virus in their faeces. Hepatitis E outbreaks often occur in developing countries due to the consumption of faeces-contaminated water, particularly during heavy rainfall and flooding [7]. Hepatitis E typically causes acute infection, although chronic infection can occur with hepatitis B and C. Symptoms of acute hepatitis E typically appear two to six weeks after exposure and include fever, nausea, abdominal pain, loss of appetite, vomiting, hepatomegaly, jaundice, itching, pale stools, and darkened urine [8]. Hepatitis E is common in young adults between 15 and 45 [9]. The overall mortality rate of hepatitis E is approximately 2%, but it can be increased, reaching 20% or more in pregnant women in some areas due to fulminant hepatic failure.

Epidemiology of HEV infection

The *Orthohepevirus* A species is a group of viruses that can infect humans and animals. Four genotypes can infect humans: HEV1, HEV2, HEV3, and HEV4. HEV1 and HEV2 primarily infect humans and are primarily spread through contamination of water sources with faecal matter, particularly following heavy rain and flooding [10,11]. These genotypes cause self-limiting acute viral hepatitis but can still present a significant public health burden in low-income countries. Person-to-person transmission of HEV1 and HEV2 is uncommon, but vertical transmission from mother to foetus during pregnancy and through blood transfusion has been reported [12,13]. HEV3 and HEV4 infections typically occur through zoonotic transmission when an individual comes into close contact with infected animals or consumes contaminated food products, particularly raw or undercooked meat. These genotypes are found in swine and wild boars, rabbits, goats, sheep, deer, horses, cats, and dogs [14-17]. Farmers, veterinarians, and individuals working in slaughterhouses may be at a higher risk of HEV infection than the general population [18,19]. HEV infection can also be transmitted through infected blood or blood products, although most iatrogenic transmissions are asymptomatic in immunocompetent individuals. In addition, transplanted organs can also transmit HEV infection [20]. There is no specific treatment for HEV infection, but the disease is usually self-limiting and resolves independently.

HEV infection in humans

Hepatitis E, also known as enterically transmitted non-A, non-B hepatitis, is a viral disease that frequently causes outbreaks in developing countries in Asia and Africa. In the past, the prevalence of HEV infection has been studied in various regions, including Asia, Europe, and America. In Asia, the seroprevalence (presence of antibodies in the blood) of HEV is estimated to be around 20-30% in China, 12-20% in Korea, and 6% in Japan [21-25]. Studies have shown that the seroprevalence of HEV tends to increase with age. For example, the detection rate of anti-HEV antibodies in children under ten is around 8%, while in individuals over 60 years old, it is 21-56% in Hong Kong and eastern China. Similarly, the seroprevalence of HEV in England and Germany is estimated to be 13-17%, with the highest prevalence occurring in individuals over 50-60 years old [26,27]. In the United States, more than 16% of blood donors have anti-HEV antibodies, and this percentage increases with age [28].

However, more recent studies have shown that the seroprevalence of HEV has decreased dramatically in most countries when compared to earlier studies. Possible explanations for the higher seroprevalence in earlier studies include small sample sizes, limited study areas, different detection kits, and different analytical methods [29]. Despite these discrepancies, most studies do report an age-dependent increase in the seroprevalence of HEV in most countries [30-33]. This suggests that subclinical HEV infections may be more common in elderly individuals. Interestingly, very high mortality rates (up to 66%) have been observed in pregnant women infected with HEV in certain regions of India [34-36]. Most of these women experience fulminant hepatic failure and have significantly higher viral loads than non-pregnant women [37]. In contrast, the mortality rate of HEV-infected pregnant women in Egypt does not differ significantly from that of non-pregnant women, despite a high prevalence of anti-HEV antibodies in this population [38]. Possible explanations for this discrepancy include less virulent strains of HEV circulating in this region and the acquisition of long-lasting immunity to HEV through early exposure to the virus. More research is needed to fully understand the impact of HEV infections on pregnant women.

HEV infection in animals

HEV is a viral infection that can cause liver disease in humans and other animals. It is prevalent in swine populations worldwide, with infections typically beginning in swine between 2 and 3 months old [39]. HEV has also been identified in various animal species, including rabbits, chickens, deer, wild boars, mongooses, rats, bats, ferrets, camels, and trout. In the United States, rates of seropositivity (a measure of exposure to the virus) for HEV were found to be 4.6% in bison, 15% in cattle, 0.9% in dogs, 0.6% in Norway rats, 41.2% in farmed swine, and 2.9% in wild swine [40]. In India, seropositivity rates ranged from 4.4% to 6.9% in cattle, from 22.7% in dogs, and from 2.1% to 21.5% in rodents, with high rates of seropositivity also seen in swine (54.6% to 74.4%) [41]. HEV has also been identified in rabbits, with 57% of rabbits in China found to be seropositive for the virus [42]. In addition, evidence of an abortion, vertical transmission of HEV, and high mortality rates in pregnant rabbits infected with rabbit HEV have been found [43]. The risk of zoonotic transmission (transmission from animals to humans) of HEV is a concern, as humans can become infected through contact with infected animals or contaminated food or water. It is crucial for individuals working with or handling animals to practice good hygiene to reduce the risk of infection.

HEV diagnosis

The diagnosis of hepatitis E infection in humans, swine, and chickens requires laboratory testing, with PCR and ELISA being the most commonly used methods [44,45]. However, the specific tests used to diagnose HEV infection vary based on the species and

the availability of reagents and test kits. In addition, the specificity of these tests for detecting HEV in different regions may vary due to the genetic heterogeneity of HEV strains. It is essential for healthcare providers and veterinarians to be aware of the different methods and limitations of HEV testing in order to diagnose and treat HEV infection accurately.

HEV prevention and control

HEV infection is a significant global health concern that requires ongoing research and prevention efforts. While a vaccine may not currently be available for humans [46], taking preventive measures such as practising good hygiene and avoiding the consumption of potentially contaminated food and water can help reduce the risk of infection. Additionally, developing vaccines for swine and avian HEV could help protect both humans and animals from the negative consequences of HEV infection. Individuals and industries must remain aware of the risks and take necessary precautions to prevent the spread of this virus.

Conclusion

Hepatitis E is increasingly recognised as a zoonotic viral disease, meaning it can be transmitted between animals and humans. The presence of HEV antibodies and the isolation of the virus in both humans and animals suggest that HEV infections may be widespread. Humans typically become infected with HEV by consuming contaminated water or undercooked animal meat. However, the transmission of HEV through blood transfusions and the development of chronic hepatitis E in solid organ transplant patients are emerging concerns. It typically causes acute infection and has symptoms including fever, nausea, and jaundice, with a mortality rate of around 2% but can be higher in pregnant women. The epidemiology of HEV infection varies depending on the genotype, with person-to-person transmission being uncommon but possible through vertical transmission during pregnancy and blood transfusion and zoonotic transmission through contact with infected animals or consumption of contaminated food products being more common. There is no specific treatment for hepatitis E currently, and prevention efforts focus on improving sanitation and hygiene and avoiding consuming contaminated food and water. In addition, using HEV vaccines in animals could help decrease the potential transmission of HEV from animals to humans.

References

1. Emerson SU, Purcell RH (2003) Hepatitis E virus. Rev Med Virol 13(3): 145-154.
2. Arankalle VA, Tsarev SA, Chadha MS, Alling DW, Emerson SU, et al. (1995) Age-specific prevalence of antibodies to hepatitis A and E viruses in Pune, India, 1982 and 1992. J Infect Dis 171(2): 447-450.
3. Meng X-J, Purcell RH, Halbur PG, Lehman JR, Webb DM, et al. (1997) A novel virus in swine is closely related to the human hepatitis E virus. Proc Natl Acad Sci 94(18): 9860-9865.
4. Haqshenas G, Shivaprasad H, Woolcock P, Read D, Meng X (2001) Genetic identification and characterization of a novel virus related to human hepatitis E virus from chickens with hepatitis–splenomegaly syndrome in the United States. J Gen Virol 82(10): 2449-2462.
5. Smith DB, Simmonds P, , Jameel S, Emerson SU, Harrison TJ, Meng X, et al. (2014) Consensus proposals for classification of the family Hepeviridae. J Gen Virol 95(10): 2223-2232.
6. Tam AW, Smith MM, Guerra ME, Huang C-C, Bradley DW, et al. (1991) Hepatitis E virus (HEV): Molecular cloning and sequencing of the full-length viral genome. Virology 185(1): 120-131.
7. Aggarwal R (2013) Hepatitis E: epidemiology and natural history. J Clin Exp Hepatol 3(2): 125-133.
8. Mirazo S, Ramos N, Mainardi V, Gerona S, Arbiza J (2014) Transmission, diagnosis, and management of hepatitis E: an update. Hepat Med 6: 45-59.
9. Kumar S, Subhadra S, Singh B, Panda B (2013) Hepatitis E virus: the current scenario. Int J Infect Dis 17(4): e228-e233.
10. Viswanathan R (1957) A review of the literature on the epidemiology of infectious hepatitis. Indian J Med Res 45: 145-155.
11. Naik S, Aggarwal R, Salunke P, Mehrotra N (1992) A large waterborne viral hepatitis E epidemic in Kanpur, India. Bull World Health Organ 70(5): 597-604.
12. Khuroo MS, Kamili S, Yattoo GN (2004) Hepatitis E virus infection may be transmitted through blood transfusions in an endemic area. J Gastroenterol Hepatol 19(7): 778-784.
13. Khuroo M, Kamili S, Khuroo M (2009) Clinical course and duration of viremia in vertically transmitted hepatitis E virus (HEV) infection in babies born to HEV-infected mothers. J Viral Hepat 16(7): 519-523.
14. Doceul V, Bagdassarian E, Demange A, Pavio N (2016) Zoonotic hepatitis E virus: classification, animal reservoirs and transmission routes. Viruses 8(10): 270.
15. Schlosser J, Eiden M, Vina-Rodriguez A, Fast C, Dremsek P, et al. (2014) Natural and experimental hepatitis E virus genotype 3-infection in European wild boar is transmissible to domestic pigs. Vet Res 45(1): 121.
16. Izopet J, Dubois M, Bertagnoli S, Lhomme S, Marchandeau S, et al. (2012) Hepatitis E virus strains in rabbits and evidence of a closely related strain in humans, France. Emerg Infect Dis 18(8): 1274-1281.
17. Yan B, Zhang L, Gong L, Lv J, Feng Y, et al. (2016) Hepatitis E virus in yellow cattle, Shandong, Eastern China. Emerg Infect Dis 22(12): 2211-2212.
18. Terio V, Bottaro M, Pavoni E, Losio M, Serraino A, et al. (2017) Occurrence of hepatitis A and E and norovirus GI and GII in ready-to-eat vegetables in Italy. Int J Food Microbiol 249: 61-65.
19. Maunula L, Kaupke A, Vasickova P, Söderberg K, Kozyra I, et al. (2013) Tracing enteric viruses in the European berry fruit supply chain. Int J Food Microbiol 167(2): 177-185.
20. Schlosser B, Stein A, Neuhaus R, Pahl S, Ramez B, et al. (2012) Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient. J Hepatol 56(2): 500-502.
21. Ahn J-m, Kang S-G, Lee D-Y, Shin SJ, Yoo HS (2005) Identification of novel human hepatitis E virus (HEV) isolates and determination of the seroprevalence of HEV in Korea. J Clin Microbiol 43(7): 3042-3048.
22. Chiu DM, Chan MC, Yeung AC, Ngai KL, Chan PK (2013) Seroprevalence of hepatitis E virus in Hong Kong, 2008–2009. J Med Virol 85(3): 459-461.
23. Choi I-S, Kwon H-J, Shin N-R, Yoo HS (2003) Identification of swine hepatitis E virus (HEV) and prevalence of anti-HEV antibodies in swine and human populations in Korea. J Clin Microbiol 41(8): 3602-3608.
24. Dong C, Dai X, Shao J-S, Hu K, Meng J-H (2007) Identification of genetic diversity of hepatitis E virus (HEV) and determination of the seroprevalence of HEV in eastern China. Arch Virol 152(4): 739-746.

25. Taniguchi M, Kim SR, Mishiro S, Takahashi K, Shin MH, et al. (2009) Epidemiology of hepatitis E in northeastern China, South Korea and Japan. J Infect 58(3): 232-237.

26. Faber MS, Wenzel JJ, Jilg W, Thamm M, Höhle M, et al. (2012) Hepatitis E virus seroprevalence among adults, Germany. Emerg Infect Dis 18(10): 1654-1657.

27. Ijaz S, Vyse AJ, Morgan D, Pebody RG, Tedder RS, et al. (2009) Indigenous hepatitis E virus infection in England: more common than it seems. J Clin Virol 44(4): 272-276.

28. Xu C, Wang RY, Schechterly CA, Ge S, Shih JW, et al. (2013) An assessment of hepatitis E virus (HEV) in US blood donors and recipients: no detectable HEV RNA in 1939 donors tested and no evidence for HEV transmission to 362 prospectively followed recipients. Transfusion 53(10pt2): 2505-2511.

29. Ditah I, Ditah F, Devaki P, Ditah C, Kamath PS, et al. (2014) Current epidemiology of hepatitis E virus infection in the United States: low seroprevalence in the National Health and Nutrition Evaluation Survey. Hepatology 60(3): 815-822.

30. Jia Z, Yi Y, Liu J, Cao J, Zhang Y, et al. (2014) Epidemiology of hepatitis E virus in China: Results from the third national viral hepatitis prevalence survey, 2005–2006. PloS one 9(10): e110837.

31. Juhl D, Baylis SA, Blümel J, Görg S, Hennig H (2014) Seroprevalence and incidence of hepatitis E virus infection in G erman blood donors. Transfusion 54(1): 49-56.

32. Takeda H, Matsubayashi K, Sakata H, Sato S, Kato T, et al. (2010) A nationwide survey for prevalence of hepatitis E virus antibody in qualified blood donors in Japan. Vox Sang 99(4): 307-313.

33. Yoon Y, Jeong HS, Yun H, Lee H, Hwang Y-S, et al. (2014) Hepatitis E Virus (HEV) Seroprevalence in the general population of the Republic of Korea in 2007–2009: a nationwide cross-sectional study. BMC Infect Dis 14: 517.

34. Jilani N, Das BC, Husain SA, Baweja UK, Chattopadhya D, et al. (2007) Hepatitis E virus infection and fulminant hepatic failure during pregnancy. J Gastroenterol Hepatol 22(5): 676-682.

35. Kumar A, Beniwal M, Kar P, Sharma J, Murthy N (2004) Hepatitis E in pregnancy. Int J Gynecol Obstet 85(3): 240-244.

36. Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK (2007) Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. Ann Intern Med 147(1): 28-33.

37. Kar P, Jilani N, Husain SA, Pasha ST, Anand R, et al. (2008) Does hepatitis E viral load and genotypes influence the final outcome of acute liver failure during pregnancy? Am J Gastroenterol 103(10): 2495-2501.

38. Stoszek SK, Abdel-Hamid M, Saleh DaA, Kafrawy SE, Narooz S, et al. (2006) High prevalence of hepatitis E antibodies in pregnant Egyptian women. Trans R Soc Trop Med Hyg 100(2): 95-101.

39. Meng XJ, Dea S, Engle RE, Friendship R, Lyoo YS, et al. (1999) Prevalence of antibodies to the hepatitis E virus in pigs from countries where hepatitis E is common or is rare in the human population. J Med Virol 59(3): 297-302.

40. Dong C, Meng J, Dai X, Liang J-H, Feagins AR, et al. (2011) Restricted enzooticity of hepatitis E virus genotypes 1 to 4 in the United States. J Clin Microbiol 49(12): 4164-4172.

41. Arankalle V, Joshi M, Kulkarni A, Gandhe S, Chobe L, et al. (2001) Prevalence of anti-hepatitis E virus antibodies in different Indian animal species. J Viral Hepat 8(3): 223-227.

42. Zhao C, Ma Z, Harrison TJ, Feng R, Zhang C, et al. (2009) A novel genotype of hepatitis E virus prevalent among farmed rabbits in China. J Med Virol 81(8): 1371-1379.

43. Xia J, Liu L, Wang L, Zhang Y, Zeng H, et al. (2015) Experimental infection of pregnant rabbits with hepatitis E virus demonstrating high mortality and vertical transmission. J Viral Hepat 22(10): 850-857.

44. Meng X, Shivaprasad H, Payne C (2008) Avian hepatitis E virus infections. Diseases of poultry, 12th ed Wiley-Blackwell, Ames, IA, 441-448.

45. Huang F, Haqshenas G, Shivaprasad H, Guenette D, Woolcock P, et al. (2002) Heterogeneity and seroprevalence of a newly identified avian hepatitis E virus from chickens in the United States. J Clin Microbiol 40(11): 4197-4202.

46. Shrestha MP, Scott RM, Joshi DM, Mammen Jr MP, Thapa GB, et al. (2007) Safety and efficacy of a recombinant hepatitis E vaccine. N Engl J Med 356(9): 895-903.

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