

Current Status of Hepatitis E Virus Infection in Korea

Sook-Hyang Jeong

Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

Hepatitis E virus (HEV) is an emerging pathogen associated with acute viral hepatitis, and HEV is becoming increasingly recognized. Approximately 2% of acute viral hepatitis is caused by HEV, and 18 cases of hepatitis E have been reported in Korea. Of these cases, only two have involved a history of travel from India, which suggests that they were imported cases. The remaining reported cases include a sporadic case of acute hepatitis E with genotype 4 HEV isolates and identification of the full genome sequence, as well as another case of genotype 4 HEV hepatitis that developed after ingestion of the raw bile juice of a wild bear living on a mountain in southern Korea. Moreover, genotype 3 HEV, which shows close genetic homology with swine HEV in Korea, has been detected in collected human serum samples. Therefore, genotypes 3 and 4 HEV are currently circulating in the Korean community and may be related to zoonotic transmission and food-borne infection. The reported anti-HEV seroprevalence of 17% to 27% in the Korean population suggests that HEV infection has been autochthonously circulating, thereby resulting in subclinical infection in Korea. Given the discrepancies among anti-HEV assays, the diagnosis of hepatitis E should be made with caution using adequate antibody assays, and HEV RNA should be preferably detected from the stool. Further virological characterization and epidemiological study of the virus are warranted. (**Gut Liver 2011;5:427-431**)

Key Words: Hepatitis E virus; Korea; Epidemiology; Genotype; Swine

INTRODUCTION

Hepatitis E virus (HEV) is a nonenveloped, single stranded, positive sense RNA virus classified as *Hepeviridae* family, *Hep-*

evirus genus, and an emerging pathogen of acute viral hepatitis with increasing recognition of the virus.¹ The epidemiology of HEV infection can be divided into 2 patterns: outbreak pattern in areas of high endemicity, mostly via water-borne or fecal-oral transmission, and a sporadic pattern worldwide, mostly via zoonotic transmission and food borne transmission.² Clinical features are mostly indicative of typical acute hepatitis; however, it can show progression to chronic hepatitis or liver cirrhosis in immunocompromized hosts.³ Specific treatments are lacking and therapy is supportive.

Although several cases of imported and autochthonous hepatitis E have been reported in Korea, the virological characterization of HEV in these case series had not been documented. Seroprevalence data reported in a few studies suggests that HEV has been circulating for a long time in the Korean community;⁴ however, it has been underdiagnosed due to underrecognition of the disease, and limited availability of diagnostic tools. This review will contain a brief overview of HEV infection and the current status of HEV infection in Korea.

HEV

The HEV genome is approximately 7.2 kb long with three open reading frames (ORF). ORF1 and 3 encode nonstructural proteins contributing to HEV replication and pathogenesis, whereas ORF 2 encodes the viral structural protein, capsid, which is the target for specific immune response.¹ According to the results of *in vitro* studies using HEV-like particles, the capsid protein contains receptor-binding domains and neutralizing epitopes.² HEV has a single serotype, but is further classified into four major genotypes, including genotype 1 (Burma), 2 (Mexico), 3 (USA), and 4 (China), indicated as the originally identified viral isolates, while the most widely distributed type is genotype 3.⁵ The crystal structure of HEV-like particles from genotype 3

Correspondence to: Sook-Hyang Jeong

Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 300 Gumi-dong, Bundang-gu, Seongnam 463-707, Korea

Tel: +82-31-787-7039, Fax: +82-31-787-7042, E-mail: jsh@snuh.org

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strains showed a different folding pattern of the capsid protein from that of genotype 1 strains.⁶

EPIDEMIOLOGY OF HEV INFECTION

Global distribution of HEV infection follows socioeconomic status. Highly endemic areas with higher than 20% anti-HEV prevalence include Central and South East Asia, including India, Malaysia, and China, as well as North Africa and the Middle East, including Egypt and Saudi Arabia. In low endemic areas, swine and human HEV strains show extremely close genetic relatedness, and special populations, including veterinarians, butchers, persons handling animal meat, and consumers of undercooked swine or wild deer meat have shown significantly higher seroprevalence than members of the general population.^{2,5,7} These findings indicate zoonotic transmission of HEV. Therefore, the epidemiology of HEV infection can be divided into 2 patterns: outbreak pattern and sporadic pattern. The outbreak pattern occurs primarily in highly endemic areas, where large epidemic episodes are intervening in the continuous endemicity, mostly via water-borne or fecal-to-oral transmission among human reservoirs. The sporadic pattern occurs worldwide, mostly via zoonotic transmission and food borne transmission.⁷ In addition, parenteral transmission via blood transfusion, organ transplantation, or mother-to child transmission has been described.⁸

CLINICAL MANIFESTATIONS OF HEPATITIS E INFECTION

Clinical features of HEV infection range from asymptomatic hepatitis to severe, fulminant hepatitis, which can result in liver-related mortality. Typical symptoms include fever, nausea, vomiting, general weakness, and jaundice lasting for 1 to 6 weeks after an incubation period of 2 to 6 weeks.¹ Hepatitis E superinfection with underlying stable chronic liver disease can present as acute hepatic decompensation. However, presence of immunoglobulin G (IgG) anti-HEV in patients with chronic liver disease did not differ from that of healthy blood donors. Moreover, previous exposure to HEV did not result in different outcomes among patients with chronic liver diseases.⁹ HEV causes self-limited, acute hepatitis in immunocompetent hosts. However, persistent HEV infection accompanied by chronic hepatitis and liver cirrhosis has been documented in immunocompromised hosts, such as organ transplantation recipients (liver, kidney, or pancreas) and HIV infected patients.^{3,10}

Hepatitis E in pregnancy has been reported to result in significantly higher mortality than in nonpregnant women, especially in India or Parkistan, where genotype 1 and 2 HEV are prevalent. Patra *et al.*¹¹ reported that HEV infected icteric, pregnant women showed a significantly higher rate of fulminant hepatitis (55%), maternal mortality (41%), poorer fetal outcome (79%), and lower live birth (21%) than those of icteric, pregnant wom-

en with nonHEV acute viral hepatitis (20%, 7%, 51%, and 49%, respectively). The mechanism of severe outcomes of HEV infection in pregnancy has not been elucidated; however, pregnancy induced suppression of T cell immunity and T helper 2 (Th2) skewed cytokine patterns as well as increased viral load may be related to poor outcomes.¹² However, HEV infected pregnant women in the other endemic area of Egypt, where genotype 3 is prevalent, did not show different outcomes from those of non-pregnant women. Moreover, no difference in outcome was observed between pregnant and nonpregnant animals in experimentally infected animals. Further study of the mechanism of pathogenesis during pregnancy is warranted.¹²

DIAGNOSIS OF HEPATITIS E

Diagnosis of hepatitis E was made by observance of typical symptoms with elevated aminotransferases, presence of IgM anti-HEV, and rising titer of IgG anti-HEV in exclusion of other etiology of acute hepatitis. Although positive detection of HEV RNA in serum or stool is a confirmatory diagnostic test, there is no commercially available HEV RNA detection assay. Enzyme immunoassays (EIA) for HEV antibodies are based on detection of antibodies against the highly conserved capsid protein. Immunoglobulin M (IgM) anti-HEV appears during the early stage of infection, and is detectable at 1 to 3 weeks after acute infection of immune-competent patients, while seroconversion may be delayed up to 6 to 10 months in immunocompromised patients.

There are several anti-HEV assays; however, the performance of each anti-HEV assay has not been well studied. Mast *et al.*¹³ reported highly discrepant results among the different assays, which suggested that diagnosis of HEV infection using anti-HEV tests should be made with caution. Genelabs anti-HEV EIA (Genelabs Diagnostics Pte. Ltd., Singapore), the most popular assay, showed good sensitivity (86.7%) for assay of IgG anti-HEV, but less satisfactory sensitivity (53.3%) for IgM anti-HEV EIA for diagnosis of acute hepatitis E confirmed by positive detection of HEV RNA.¹⁴ Findings from a recent study for comparison of 2 commercially available IgG anti-HEV kits (Genelabs EIA, and Wantai EIA [Wantai Biological Pharmacy Enterprise Co., Ltd., Beijing, China]) showed that Wantai EIA was more sensitive than Genelabs EIA, and remained positive for a longer time post infection.¹⁵

Detection of HEV RNA in serum or stool using nested or real-time PCR is the most sensitive and definitive diagnostic test; however, the viremic period is short (10 to 30 days after onset of symptoms) and detection of HEV RNA within the proper time for diagnosis in the clinical setting is not easy, while fecal shedding of virus may last longer with high viral titer compared to viremia in the blood.¹⁶ Although there is no commercially available HEV RNA PCR assay, diagnosis of hepatitis E should be made with repeated use of anti-HEV (both of IgM and IgG) and

preferably detection of HEV RNA in stool or blood.

HUMAN CASES OF HEPATITIS E IN KOREA

Eighteen cases of hepatitis E have been reported in Korea; these cases are summarized in Table 1.¹⁷⁻²³ Among them, only 2 cases involved a history of travel from India, suggesting imported cases, and the remaining 16 cases had no history of travel from highly endemic areas. A sporadic case of acute hepatitis E with genotype 4 HEV isolates with identification of the full genome sequence in a middle aged woman was reported.²² Another case of genotype 4 HEV hepatitis, which developed after ingestion of raw bile juice of a wild boar living on a mountain in southern Korea has recently been published, which suggests zoonotic transmission of HEV from a wild boar to a human in Korea.²³ A few studies have reported on detection of genotype 3 HEV in collected sera from several diagnostic laboratories in Korea, which was similar to the genotype identified in pigs in Korea.^{4,24} This suggests zoonotic transmission of HEV from pigs to humans in Korea; however, direct documentation of the transmission was not reported.

In a recent study of the etiology of acute viral hepatitis in Korea, among 771 patients with acute viral hepatitis, 2% were attributable to HEV, while 77% were to hepatitis A virus, 4% to hepatitis B virus, 3% to hepatitis C virus, and 8% other viruses or cryptogenic causes.²⁵ Six percent of the patients showed positive results for both IgM anti-HEV and IgM anti-hepatitis A virus (HAV), which was a peculiar finding. According to clinical, serological, and molecular comparative analyses, coexistence of both IgM anti-HEV and IgM anti-HAV was a false positive result of IgM anti-HEV measured by Genelabs HEV IgM EIA (Genelabs Diagnostics Pte. Ltd.) in the setting of hepatitis A, rather than true coinfection of HAV and HEV. Of particular interest, IgM anti-HEV measured by Wantai IgM EIA (Wantai Biological Pharmacy Enterprise Co., Ltd.) did not show such false positive results, which suggests its advantage for use in diagnosis of hepatitis E infection in the Korean population, where genotype 3 and 4 HEV circulate in the community (submitted paper).

SEROPREVALENCE OF HEV INFECTION IN KOREA

The IgG anti-HEV positive rate measured using Genelabs ELI-

Table 1. Summary of Reported Human Cases of Hepatitis E in Korea

Age, yr /Sex	Symptom/ Travel history	ALT, IU/L /Bilirubin, mg/dL	Clinical outcome	IgM anti-HEV (titer/cutoff)	IgG anti-HEV (titer/cutoff)	HEV RNA	Reference
27/M	Fever, myalgia/No	6,200/6.8	Recovery	Positive (1.22/0.45)	Positive	Not detected	Korean J Hepatol (2002)
28/F	Fever, diarrhea/India	1,776/1.7	Recovery	Positive (1.77/0.44)	Positive (4.0/0.58)	Not detected	Korean J Gastroenterol (2004)
34/F	Jaundice/No	2,330/7.9	Recovery	Positive (1.30/0.46)	Positive (1.27/0.62)	Not detected	Korean J Gastroenterol (2006)
42/M	Abdominal pain/No	690/10.6	Recovery	Positive (1.10/0.43)	Positive (3.35/0.53)	Not detected	Korean J Gastroenterol (2006)
30/M	Fatigue/No	2,492/3.3	Recovery	Positive	Negative	Not detected	Korean J Hepatol (2006)
25/F	Jaundice, fatigue/No	2,603/7.6	Recovery	Positive	Negative	Not detected	Korean J Gastroenterol (2006)
24/M	Jaundice/India	1,147/10.3	Recovery	Positive	Positive	Not detected	Korean J Gastroenterol (2006)
29/M	Jaundice/No	3,951/5.2	Recovery	Positive	Negative	Not detected	Korean J Gastroenterol (2006)
52/F	Jaundice/No	789/6.8	Recovery	Positive	Negative	Not detected	Korean J Gastroenterol (2006)
45/M	Fatigue/No	668/1.6	Recovery	Positive	Negative	Not detected	Korean J Gastroenterol (2006)
48/F	Jaundice/No	1,582/11.2	Recovery	Positive	Negative	Not detected	Korean J Gastroenterol (2006)
42/F	Jaundice/No	936/7.3	Recovery	Positive	Negative	Not detected	Korean J Gastroenterol (2006)
23/F	Jaundice/No (underlying autoimmune hepatitis)	121/40.9	Liver transplantation	Positive	Negative	Not detected	Korean J Gastroenterol (2006)
42/F	Fever/No	216/1.0	Recovery	Positive	Not detected	Not detected	Korean J Gastroenterol (2007)
33/M	Fatigue/No	316/9.5	Recovery	Positive	Not detected	Not detected	Korean J Gastroenterol (2007)
40/F	Fatigue/No	236/0.5	Recovery	Positive	Not detected	Not detected	Korean J Gastroenterol (2007)
51/F	Jaundice/No	2,643/2.2	Recovery	Positive	Positive	Detected, genotype 4	Arch Virol (2010)
54/M	Jaundice/No (ingestion of raw bile juice of wild boar)	1,328/4.7	Recovery	Positive (3.62/0.30)	Positive (3.73/0.38)	Detected, genotype 4	J Clin Virol (2011)

HEV, hepatitis E virus.

SA has been reported as 17.7% in 96 serum samples from blood donors collected in 1995, and 11.9% in 361 serum samples collected from several diagnostic laboratories in medical health promotion centers.^{4,24} Comparison of seroprevalence of HEV in adults older than 40 years in China, Korea, and Japan showed the highest rate (50.7%) in China, 34% in Korea, and 6% in Japan, which was measured using the Japanese EIA kit.²⁶ In developed countries, reported HEV data on seroprevalence range from 0.26% to 31%. Although seroprevalence reflects previous exposure to HEV infection, detection methods or assays for anti-HEV IgG vary in their performance, and comparison of seroprevalence among different populations is meaningful only when using a properly validated detection method. A recent comparative study of the performance of 2 commercial assays (Genelabs and Wantai HEV IgG EIA kits) showed that HEV seroprevalence data using the Genelabs assay had underestimated the true figure, compared with the Wantai assay, which was positive in more sera from proven cases, and remained positive for a longer time post infection.¹⁵

In the meantime, anti-HEV prevalence in pigs in Korea has been reported as 14.8%, and HEV RNA positivity among pigs has been reported as 2.3% to 10.8%, which showed genetic homology with swine and human HEV isolates in the United States and Japan (92.5% to 97%), and phylogenetic tree analysis indicated genotype 3.^{24,27} A recent study reported an HEV RNA detection rate of 55% in pigs from an isolated region of Korea, Jeju island.²⁸ In addition, HEV RNA was detected in live oysters collected in various areas of Korea (14/161 samples, 8.7%),^{29,30} and was confirmed as genotype 3.

TREATMENT AND VACCINES FOR HEPATITIS E

There is no specific antiviral therapy for hepatitis E, and supportive care is the main therapy. However, specific antiviral treatment is required in severe or persistent hepatitis in immunocompromised hosts. Kamar *et al.*³⁰ reported that pegylated interferon could induce sustained virological response in the post-transplantation setting.

To date, 2 types of HEV vaccine have been developed. The first vaccine produced by GlaxoSmithKline is a genotype 1 recombinant HEV protein vaccine prepared by a recombinant baculovirus system containing capsid antigen with aluminium hydroxide as an adjuvant; the vaccine efficacy was reported as 95.5% after three doses in a phase 2 clinical trial including 5,323 members of the Nepalese Army and the U.S. Army.³¹ The second HEV vaccine (HEV239, Hecolin), which is a genotype 1 recombinant HEV capsid protein vaccine prepared by a recombinant *E. coli* system and adsorbed with aluminium hydroxide, was developed by Xiamen Innovax Biotech in China; the vaccine efficacy after 3 doses was reported as 100% in a phase 3 trial including 11,165 Chinese participants.³² Travelers from areas of low-endemicity to highly endemic areas should be protected

from HEV infection using the above vaccines. Although universal vaccination of children in highly endemic areas would be highly effective, specific programs or strategies for HEV vaccination should be developed.

CONCLUSIONS

HEV is a rare cause of acute viral hepatitis in Korea, which has shown a sporadic, nonendemic epidemiological pattern. Clinical features of hepatitis E appear to be relatively mild, compared to hepatitis A, and the viremic period in human cases appears to be short, which causes difficulty in detection of HEV RNA in serum samples. Genotype 3 and 4 HEV are circulating in Korean communities, which may be related to zoonotic transmission and food-borne infection. Seroprevalence of 17% to 27% suggests that HEV infection has been autochthonously circulating in Korea with commonly subclinical infection. Diagnosis of hepatitis E should be made with caution using adequate antibody assays and detection of HEV RNA, preferably in stool. Further study of the epidemiology and virologic characterization of HEV is warranted.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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