Review Article

Hepatitis E Virus Infection: A Zoonotic Threat

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Abstract | Hepatitis E is a virus mediated liver disease caused by hepatitis E virus (HEV). There are an estimated 3 million cases of acute HEV infection every year, causing 70,000 hepatitis E-related deaths worldwide. HEV is transmitted via the fecal-oral route. Contaminated water and food are main source of infection. HEV is classified in the family *Hepeviridae* and divided in four putative genera. Genotype 1 and 2 are associated with epidemics in East and South Asia and restricted to humans, whereas genotypes 3 and 4 are zoonotic and associated with cluster cases of hepatitis E in developed countries. HEV strains were isolated from variety of animals and the demonstrated ability of cross-species infection by some of these animal strains have broadened the host range and raised the concern of zoonosis. Pigs, deer and other animal species may serve as a reservoir for HEV. This review highlights the current understanding of HEV infection in humans and animals.

Keywords | Hepatitis, Hepatitis E, Hepatitis E virus, Liver Disease, Zoonosis

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INTRODUCTION

Hepatitis E, first recognized as non-A and non-B hepatitis more than three decades ago, is characterized by an acute hepatitis and poses a serious threat to human and animal health. According to a recent estimate each year there are more than 3 million symptomatic cases of acute hepatitis E, resulting in approximately 70,000 deaths worldwide (Rein et al., 2012). Hepatitis E is mainly attributed to poor hygienic conditions and consumption of contaminated or insufficiently treated drinking water (Benjelloun et al., 1997; Coursaget, et al., 1998a; Guthmann et al., 2006). Outbreaks of waterborne hepatitis E had been observed following heavy rainfall and flooding in endemic regions (Corwin et al., 1996; Piper-Jenks et al., 2000). However, on account of better hygiene and quality of water supply, industrialized countries were considered HEV free or non-endemic for HEV; but isolated incidence of disease outbreaks were reported in developed countries (Hoofnagle et al., 2012). Hepatitis E is self-limiting, i.e. gets cured without medical intervention, in immunocompetent individuals causing <2% mortality, but in immunocompromised patients chronic hepatitis could be induced and among pregnant women mortality could be high (10-30%) (Kumar et al., 2004b). Disease pathogenesis, though not fully understood, can lead to acute liver failure, chronic infection, or extrahepatic symptoms (Krain et al., 2014).

The causative agent, hepatitis E virus (HEV), is classified into the genus *Hepevirus* and family *Hepeviridae*. A new taxonomic scheme for the family *Hepeviridae* has recently been proposed (Smith et al., 2014). HEV genomic RNA is comprised of a short 5` non-coding

region (NCR), three open reading frames (ORFs), and a 3` NCR. ORF1 encodes a polyprotein which is purportedly processed into methyltransferase domain, Y domain, papain-like cysteine protease, proline-rich hinge domain or variable protein, X domain linked to the viral papain-like proteases, RNA helicase and RNA polymerase. A subgenomic RNA is generated during viral replication which encodes ORF2, a capsid protein and ORF3, a small phosphorylated protein (Tam et al., 1991; Koonin et al., 1992; Holla et al., 2013).

HEV has been isolated and characterized from humans and variety of other animal species ranging from bats, chicken, camel, cutthroat trout, deer, ferret, fox, mink, mongoose, moose, pig, rabbit, rat and wild boar (Meng, 2010a; Meng, 2010b; Meng, 2011; Meng, 2013). With this expanding host range and diversity, hepatitis E is now recognized as a zoonotic disease for which animals like bats, pigs and other animal species may serve as reservoirs. Successful transmission of swine HEV to macaques and cases of acute and sometimes fatal hepatitis E following consumption of uncooked deer or wild boar meat highlight zoonotic potential of HEV infection (Tei et al., 2003; Takahashi et al., 2004; Tei et al., 2004; Li et al., 2005). Further establishment of chronic hepatitis E, as a result of persistent HEV infection in an immunocompromised individual indicates potential huge burden on health care expenditure and warrants urgent intervention towards curtailing zoonotic transfer of HEV (Kamar et al., 2008; Kamar et al., 2011). Here emerging zoonotic risks of HEV induced hepatitis E are reviewed and a potential strategy to prevent zoonosis has been proposed.

Hepatitis E in Human

Hepatitis E in human is an acute, self-limiting illness, with symptoms generally clearing off within weeks and in some cases, within months of onset of infection. Hepatitis E is presented with symptoms related to other viral hepatitis infections in general and with those seen in acute hepatitis A in particular (Khuroo, 1980). Clinically, HEV infection is presented with combinations of symptoms such as fever, lassitude/weakness, fatigue, loss of appetite, nausea and/or vomiting, dark urine, light (clay/ash-colored) stool, hepatalgia, jaundice (yellowing of the skin and sclera) and hepatomegaly (Dalton et al., 2008; Terzic et al., 2009; Labrique et al., 2010; Aggarwal, 2011; Goumba et al., 2011) . Elevated level of alanine amino transferase, aspartate transaminase, and gamma-glutamyl transpeptidase are common indicator of hepatic infection of hepatitis E (Terzic et al., 2009; Turner et al., 2010).

HEV infections in both epidemic- and sporadic-transmission settings are mostly asymptomatic and subclinical in different geographic regions (Nicand et al., 2001; Khuroo et al., 2004; Guthmann et al., 2006; Stoszek et al., 2006; Dalton et al., 2007; Christensen et al., 2008; Begum et al., 2009; Kuniholm et al., 2009; Gad et al., 2011; Renou et al., 2011; Aggarwal, 2013). Sporadic cases of hepatitis E in industrialized countries were mainly associated with travel to endemic countries such as India, Mexico, Nepal and Pakistan (Centers for Disease Control and Prevention, 1993; Johansson et al., 1995; La Rosa et al., 2011). However, autochthonous cases of acute HEV infection in patients who had never travelled to endemic regions were also reported (Schlauder et al., 1998; Schlauder et al., 1999; Ijaz et al., 2009). Cases of HEV infections without overt symptoms were documented in organ donors (Schlosser et al., 2012) and in associates of infected patients (Renou et al., 2011). Some of the hepatitis E patients may progress to acute liver failure (ALF), also called fulminant hepatic failure, which is often fatal if onset is within 6 to 8 weeks of first symptom. Pregnant women and patients with preexisting chronic liver illnesses are at increased risk of developing ALF (Coursaget et al., 1998b; Ghoshal et al., 2001; Kumar et al., 2004a; Mamun et al., 2009). Rarely, HEV infections may be prolonged or chronic, mainly among patients with compromised immune systems and patients receiving immunosuppressive drugs during organ transplant or cancer therapy (Khuroo et al., 2004; Matsubayashi et al., 2004; Mitsui et al., 2004; Boxall et al., 2006; Colson et al., 2007; Tamura et al., 2007; Matsubayashi et al., 2008; Mansuy et al., 2009; Schlosser et al., 2012). These reports indicate that HEV infection is more prevalent than originally believed. A considerably large number of people were found to be anti-HEV antibody positive e.g. 19-21% of blood donors in USA (Thomas et al., 1997; Xu et al., 2013), 13-53% subjects studied in European countries (Ijaz et al., 2009; Mansuy et al., 2011; Romano et al., 2011; Faber et al., 2012) and 6-43% subjects studied in Asian countries (Li et al., 2006; Dong et al., 2007; Taniguchi et al., 2009; Chiu et al., 2013; Lee et al., 2013) had antibodies specific

to HEV.

Hepatitis E in animals

Bats

Drexler et al. (2012) had analysed 3,869 bat specimens from 85 different species and from five continents for hepevirus RNA. Presence of HEV RNA was confirmed in bats originating from Africa, Central America and Europe. Despite this widespread distribution of HEV in bats, none of the bat hepevirus transmission to human could be confirmed in over 90,000 human blood donations and individual patient sera, indicative of limited zoonotic potential for bat hepevirus. Based on sequence comparison a new genus for bat HEV has been proposed.

Camel

Woo et al. (2014) had detected presence of HEV RNA in fecal samples from 3 dromedary camels in Dubai, United Arab Emirates. On the basis of sequence analysis, less than 20% nucleotide similarity was found when compared with known HEV and therefore author proposed a new genus for dromedary camel HEV (dcHEV).

Chicken

At least three genotypes of HEV have been documented from chickens worldwide (Bilic et al., 2009; Marek et al., 2010). HEV infection in chickens is enzootic affecting 71% of chicken flocks in the United States. HEV infection in chickens is mostly subclinical, while 30% of chickens were seropositive for avian HEV antibodies (Huang et al., 2002; Sun et al., 2004). Though evidence of avian infection in humans is currently lacking (Huang et al., 2004), but spread of bird to bird infection had been reported (Hsu and Tsai, 2014).

Cut throat trout (Fish)

Fish HEV virus was originally described as the cutthroat trout (*Oncorhynchus clarkii*) virus (CTV) (Batts et al., 2011). CTV was isolated from spawning adult trout in the United States. Based on genome organization and nucleotide sequence virus was linked to *Hepeviridae* family. However CTV shares only 13-27% amino acid sequence identity with human or avian HEV. So far it is the only HEV isolate which could efficiently be propagated in the Chinook salmon embryo (CHSE-214) cell line.

Ferrets

Ferret strain of HEV (FRHEV) was genetically identified in the Netherlands and in the laboratory ferrets in Japan (Raj et al., 2012; Li et al., 2014). Ferret HEV isolate from the Netherlands was distinct from HEV genotype 1-4, and shared the highest nucleotide identity (72.3%) with rat HEV. Ferret HEV genome organization was also different from known HEV genotypes owing to the existence of ORF4 as an overlapping region of ORF1. FRHEV isolate from laboratory ferret in Japan shares 82.4%-82.5% nucleotide identity with the Netherlands strain and ORF2 shares 94.2%-94.8% amino acid identity, indicative of similar antigenicity.

Fox

Bodewes et al. (2013), in their attempt to study viral microbiome in red foxes (*Vulpes vulpes*), evaluated fecal samples of 13 red foxes by random PCR and sequencing. Various novel viruses, including a parvovirus, bocavirus, adeno-associated virus, hepevirus, astroviruses and picobirnaviruses, were detected. Fox hepevirus shared highest amino acid homology (73%-85%) with rat HEV.

Mink

Krog et al. (2013) had evaluated fecal and liver samples of farmed mink in Denmark. Following initial screening from 85 fecal samples of farmed mink by nested PCR they developed a RT-PCR based assay and further examined 233 samples from total 89 animals. Phylogenetic analysis of viral sequence placed farmed mink HEV together with ferret and rat HEV, with 76% and 69% nucleotide sequence identity, respectively. A 65% identity with HEV genotype 3 and 4 was identified.

Moose

Moose are common animal hunted for consumption in the whole of Scandinavia. Lin et al. (2014) examined liver sample of a three-year old deceased moose for the presence of HEV RNA. Identified sequence was highly divergent from known four HEV genotypes (1-4) with nucleotide sequence similarity of 37-63%.

Domestic Pig

Swine hepatitis E virus (swine HEV) was the first identified animal strain of HEV. It was isolated from domestic pigs in the United States (Meng et al., 1997).

Swine HEV belongs to HEV genotype 3 and 4, and was identified worldwide. HEV infection in pigs is also through fecal-oral route and fecal shedding of virus is the major source of virus for spread among both pigs as well as humans (Meng, 2013).

Wild Boar

Wild boars (*Sus scrofa*) was reported to harbor HEV in Spain (de Deus et al., 2008), Germany (Kaci et al., 2008), Italy (Martelli et al., 2008), Japan (Michitaka et al., 2007; Takahashi et al., 2011), and Australia (Chandler et al., 1999). These wild boars generally were detected to be infected with HEV genotype 3 and 4.

Rats

Rat HEV shares only 60% and 50% sequence homology with other mammalian and avian strain of HEV, respectively. Various strains of HEV were genetically identified in wild and domestic species of rat (Johne et al., 2010a; Johne et al., 2010b; Purcell et al., 2011; Johne et al., 2012). With recent identification of HEV genotype 3 strains from rats in United States, zoonotic potential of rat HEV has gained importance.

Rabbits

Rabbit HEV shares 74% nucleotide homology with HEV genotype 1, 73% with genotype 2, 78% to 79% with genotype 3, 74% to 75% with genotype 4 and 46% to 47% with avian HEV. Related HEV strains were isolated from rabbits in China (Zhao et al., 2009), United States (Cossaboom et al., 2011), and France (Izopet et al., 2012). Experimentally, rabbit HEV strain was successfully demonstrated to be transmitted to pigs, indicative of crossing species barrier (Cossaboom et al., 2012).

Other Potential Animal Reservoirs

Anti-HEV antibodies and HEV RNA amplicon were detected in other animals such as cattle, sheep, dog, deer, cat, goat and nonhuman primates (Meng, 2013). Detection of HEV infection in variety of these animal species suggest a widespread circulation of HEV and phylogenetic analysis of these virus isolates will help in comprehending the host range and existing animal reservoirs of HEV.

HEV Crossing Species Barrier

HEV genotype 1 and 2 are mostly restricted to humans as seen from unsuccessful experimental infection of pigs (Meng et al., 1998a) and goats (Sanford et al., 2013) with HEV. However, HEV genotype 3 and 4 had infected both nonhuman primates and pigs (Meng et al., 1998b; Halbur et al., 2001; Williams et al., 2001; Feagins et al., 2008). Zoonotic transmission of HEV from deer (Tei et al., 2003; Tei et al., 2004) and pet cat (Kuno et al., 2003) to humans had also been reported. Recent rise in cases of persistent HEV infection in immunocompromised patients had almost exclusively found to be infected with HEV genotype 3 (Kamar et al., 2012), suggesting zoonotic mode of infection transmission (Legrand-Abravanel et al., 2010; Moal et al., 2012).

DIAGNOSIS

As mentioned before, hepatitis E symptoms are clinically indistinguishable from other types of acute viral hepatitis. Therefore, diagnosis of HEV infection is usually based on the detection of virus specific IgA, IgG, and IgM antibodies in blood. Virus specific antibodies are generally detected against ORF2 protein based ELISA test (Ghabrah et al., 1998; Engle et al., 2002; Meng et al., 2002). Anti-HEV IgG antibody detection assay systems are commercially available from Abbott Laboratories, Wiesbaden, Germany (Abbott Immunoglobulin G Assay) and Genelabs Diagnostitics, Singapore (Genelabs IgG Assay). Both assays were found to have adequate sensitivity and specificity in a hepatitis outbreak setting (Myint et al., 2006). Detection of anti-HEV IgA and IgM is indicative of recent infection, however, detection of HEV RNA in serum, bile and/or fecal samples is the most reliable marker of an ongoing HEV infection. HEV RNA is detected by nucleic acid amplification technique-based reverse transcriptase polymerase chain reaction (RT-PCR) in a qualitative assay (presence or absence of viral RNA in a biological sample), or quantitative assay (copy number of viral RNA per ml of biological specimen). World Health Organization (WHO) established an international standard candidate for HEV RNA, code number 6329/10, formulated by using a genotype 3a HEV strain and is available in lyophilized form to be used as a positive candidate in quantitative RT-PCR assay for calculation of copy number from patient specimen (Baylis et al., 2013).

TREATMENT AND PREVENTION

As HEV is a self-limiting disease, no line of treat-

ment is available and disease prevention is the best method. In 2011, first vaccine against HEV infection, Hecolin or HEV-239, in human was licensed in China (Wu et al., 2012; Zhang et al., 2013). This vaccine is not yet available in rest of the world. In the absence of vaccine, availability of clean water and good hygiene practices such as washing hands properly and consumption of only properly cooked food will be very helpful in controlling virus spread.

PERSPECTIVE

With accumulating evidence it is clear that HEV is no more limited to only developing countries. HEV is now recognized as infectious agent affecting humans and animals and therefore posing a serious public health threat worldwide. Zoonotic transmission of HEV is the major cause of hepatitis E in developed countries. Despite presence of HEV across the world, this pathogen remains relatively neglected on the global public health stage. Lack of medical and laboratory infrastructure and lack of awareness of HEV hinders surveillance of virus spread. With recent availability of sensitive diagnostic assays it is important that all the tools, necessary to identify and respond to HEV infections, made available in different parts of the world. A detailed guideline to follow up infection cases in endemic as well as in emergency situation needs to be developed to contain virus. Active research on hepatitis E both in animal and human had given novel insights into the HEV pathogenesis, yet more work is needed to understand chronic and extra-hepatic infections to be able to determine better treatment approaches. Similarly, an understanding of disease pathogenesis in pregnant women and children will be helpful in addressing global impact of HEV. Availability of human vaccine in all parts of the world and development of an effective animal HEV vaccine is need of the hour to prevent spread of infection across different species and to human.

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