Veterinary Microbiology 140 (2010) 256–265

Contents lists available at ScienceDirect

Veterinary Microbiology

journal homepage: www.elsevier.com/locate/vetmic

Review

Hepatitis E virus: Animal reservoirs and zoonotic risk

X.J. Meng *

Center for Molecular Medicine and Infectious Diseases, Department of Biomedical Sciences and Pathobiology, College of Veterinary Medicine, Virginia Polytechnic Institute and State University, Blacksburg VA, USA

ARTICLE INFO

Article history:
Received 22 September 2008
Received in revised form 18 February 2009
Accepted 6 March 2009

Keywords:
Hepatitis E virus (HEV)
Swine HEV
Avian HEV
Zoonosis
Cross-species infection
Food safety
Pigs
Chickens

ABSTRACT

Hepatitis E virus (HEV) is a small, non-enveloped, single-strand, positive-sense RNA virus of approximately 7.2 kb in size. HEV is classified in the family *Hepeviridae* consisting of four recognized major genotypes that infect humans and other animals. Genotypes 1 and 2 HEV are restricted to humans and often associated with large outbreaks and epidemics in developing countries with poor sanitation conditions, whereas genotypes 3 and 4 HEV infect humans, pigs and other animal species and are responsible for sporadic cases of hepatitis E in both developing and industrialized countries. The avian HEV associated with Hepatitis-Splenomegaly syndrome in chickens is genetically and antigenically related to mammalian HEV, and likely represents a new genus in the family. There exist three open reading frames in HEV genome: ORF1 encodes non-structural proteins, ORF2 encodes the capsid protein, and the ORF3 encodes a small phosphoprotein. ORF2 and ORF3 are translated from a single bicistronic mRNA, and overlap each other but neither overlaps ORF1. Due to the lack of an efficient cell culture system and a practical animal model for HEV, the mechanisms of HEV replication and pathogenesis are poorly understood. The recent identification and characterization of animal strains of HEV from pigs and chickens and the demonstrated ability of cross-species infection by these animal strains raise potential public health concerns for zoonotic HEV transmission. It has been shown that the genotypes 3 and 4 HEV strains from pigs can infect humans, and vice versa. Accumulating evidence indicated that hepatitis E is a zoonotic disease, and swine and perhaps other animal species are reservoirs for HEV. A vaccine against HEV is not yet available.

Contents

1. Introduction . . . 257
2. History . . . 257
   2.1. Human HEV . . . 257
   2.2. Swine HEV . . . 257
   2.3. Avian HEV . . . 258
3. The infectious agent . . . 258
   3.1. Virion properties . . . 258
   3.2. Classification . . . 258
   3.3. Genome organization . . . 258
   3.4. Replication strategy . . . 259

* Tel.: +1 540 231 6912; fax: +1 540 231 3426.
E-mail address: xjmeng@vt.edu.

0378-1135/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.vetmic.2009.03.017

4. Diseases in animals and man . . . 260
4.1. Epidemiology . . . 260
4.2. Clinical signs and pathological lesions . . . 260
4.3. Hepatitis E as a zoonotic disease . . . 261
4.4. Cross-species infections by HEV . . . 262
5. Diagnosis . . . 262
6. Prevention and control . . . 263
7. Conclusions . . . 263
8. Future prospects . . . 263
References . . . 264

1. Introduction

Hepatitis E accounts for a significant proportion of enterically transmitted form of viral hepatitis in humans (Purcell and Emerson, 2001). The disease is an important public health problem in many developing countries of Asia and Africa, and is also endemic in many industrialized countries including the United States and several European countries (Meng, 2008). Although the overall mortality of hepatitis E is less than 1% in the general population, it can reach up to 28% in infected pregnant women (Purcell and Emerson, 2001). The causative agent, hepatitis E virus (HEV), is transmitted primarily via the fecal–oral route through contaminated water or food. In industrialized countries, acute cases of hepatitis E were reported in travelers returning from endemic regions although sporadic cases have also been reported in patients with no known epidemiological risk factors (Clemente-Casares et al., 2003). In developing countries with poor sanitation conditions, rare outbreaks of acute hepatitis E in more explosive epidemic form are generally associated with fecal contamination of drinking water (Arankalle et al., 1995; Purcell and Emerson, 2001).

The recent discoveries of animal strains of HEV, swine hepatitis E virus (swine HEV) from pigs in 1997 (Meng et al., 1997) and avian hepatitis E virus (avian HEV) from chickens in 2001 (Haqshenas et al., 2001), and the existence of other animal species that are seropositive for IgG anti-HEV (Meng, 2006; Meng and Halbur, 2006; Meng et al., 2008), have broadened the host ranges and diversity of the virus. Accumulating evidences indicate that hepatitis E is a zoonotic disease, and domestic pigs, wild boars and maybe other animal species are reservoirs for HEV. The ubiquitous nature of the virus in domestic pigs and wild boars as well as in other animal species raises public health concern for zoonosis and food safety.

2. History

2.1. Human HEV

In 1980, seroepidemiological studies of waterborne epidemics of hepatitis originally thought to be caused by hepatitis A virus (HAV) in India revealed that the patients were negative for antibodies to HAV, thus providing evidence for the existence of a new form of enterically transmitted viral hepatitis which was later designated as hepatitis E (Purcell and Emerson, 2001). Successful transmission of viral hepatitis E to a human volunteer via fecal–oral route with a stool sample collected from a hepatitis E patient was demonstrated in 1983, and virus-like particles were detected in the stool of the infected volunteer (Balayan et al., 1983). However, the causative agent, hepatitis E virus (HEV), was not identified until 1990 when its complete genome was cloned and sequenced (Tam et al., 1991). Thus far HEV still could not be efficiently propagated in cell culture system, and this has greatly hindered our understanding of its biology and pathogenesis.

2.2. Swine HEV

Balayan et al. (1990) reported an experimental infection of domestic swine with an Asian strain of human HEV, and thus providing the first experimental evidence of HEV infections in pigs. However, a retrospective study revealed that the virus infecting the pigs in that study was not a human HEV but rather a strain of swine origin (Lu et al., 2004). Subsequently, two independent laboratories in the United States failed to reproduce HEV infections in pigs using a well-characterized genotype 1 Asian strain (Sar-55) and a genotype 2 Mexican strain (Mex-14) of human HEV (Meng, 2003). Detections of HEV antibodies and RNA were also reported from pigs in Nepal in 1995, although the identity of the virus infecting the Nepalese pigs was not known (Clayson et al., 1995). In 1997, the first animal strain of HEV, swine HEV, was identified and characterized from pigs in the United States (Meng et al., 1997). The authors serendipitously found out that the majority of adult pigs in the United States were positive for IgG anti-HEV, suggesting that the pigs were exposed to a HEV-related agent. To identify the agent responsible for the seropositivity in pigs, a prospective study was conducted in a commercial swine farm in Illinois (Meng et al., 1997). Twenty piglets born to both IgG anti-HEV seronegative and seropositive sows in a swine farm were monitored for more than 5 months for evidence of HEV infection. By 21 weeks of age, 16 of the 20 piglets monitored in this prospective study had seroconverted to IgG anti-HEV, and subsequently a novel virus genetically and antigenically closely related to human HEV, designated swine HEV, was molecularly cloned and characterized from the naturally infected piglets. Koch's postulates were fulfilled as specific-pathogen-free (SPF) pigs were experimentally infected with swine HEV, and