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Review

Risk of zoonotic transmission of HEV from rabbits

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ABSTRACT

Hepatitis E virus strains from rabbits indicate that these mammals may be a reservoir for HEVs that cause infection in humans. Further issues remain to be clarified, including whether the genotype of rabbit HEV differs from human and swine HEV genotype 3 and whether rabbit HEV can infect human and other animals.

HEV was found in farmed rabbits in several geographic areas of China, in USA and more recently in France. The prevalence of antibodies against HEV was 36%, 57% and 55% in rabbits from Virginia (USA), Gansu Province and Beijing (China), respectively. HEV RNA was detected in 16.5% of serum samples from farmed rabbits in Virginia, 7.5% in Gansu Province and 7.0% in Beijing. HEV RNA was detected in 7% of bile samples from farmed rabbits and in 23% of liver samples from wild rabbits in France. The full-length genomic sequences analysis indicates that all the rabbit strains belong to the same clade. Nucleotide sequences were 72.2–78.2% identical to HEV genotypes 1–4. Comparison with HEV sequences of human strains circulating in France and reference sequences identified a human strain closely related to rabbit HEV. A 93-nucleotide insertion in the X domain of the ORF1 of the human strain and in all the rabbit HEV strains was found. Moreover, the ability of rabbit HEV to cause cross-species infection in a pig model has recently been demonstrated. Rabbit HEV can replicate efficiently in human cell lines. Collectively, these data support the possibility of zoonotic transmission of HEV from rabbits.

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1. Introduction

Hepatitis E virus (HEV) is a major cause of acute hepatitis in many developing countries in Asia and Africa where it is transmitted by the fecal–oral route due to poor sanitation.¹ Acute hepatitis E is also increasingly reported in industrialized countries where the transmission is mainly zoonotic.^{2,3} The initial discovery of HEV transmission from domestic pigs⁴ has been followed by evidence

Abbreviation: HEV, hepatitis E virus.

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that other mammals like wild boar and deer are also potential reservoirs of HEV.⁵

The course of HEV infections is generally self-limiting and asymptomatic. Fulminant hepatitis can occur in pregnant women and people with underlying liver disease.^{6–8} Symptomatic infection may be misdiagnosed. For instance, HEV can be mistaken for drug-induced liver injury.^{9,10} Extra hepatic manifestations have also been described in association with HEV infection. For instance, neurological manifestations can occur occasionally in patients with hepatitis E infection.^{11,12} HEV infections can become chronic in immunocompromised patients, such as recipients of solid-organ transplants,^{13–15} those with hematological diseases,^{16–18} and patients infected with the human immunodeficiency virus.^{19–21}

HEV is a positive-sense, single-stranded RNA non-enveloped virus. It is a member of the genus *Hepevirus* in the family *Hepeviridae*.²² The HEV genome is approximately 7.2 kb long and contains three open reading frames (ORFs) as well as 5' and 3' untranslated regions. ORF1 encodes non-structural proteins, with putative functional domains including methyltransferase, papain-like cysteine protease (PCP), helicase and RNA-dependent RNA polymerase (RdRp) domains. Besides these, other domains are homologous to other plant and animal positive-strand RNA viruses: Y domain, X or macro domain and the polyproline region (PPR). ORF2 encodes the capsid protein, and ORF3 encodes a small phosphoprotein. Although all HEV isolates are believed to belong to a single serotype,²³ phylogenetic analysis of HEV sequences has led to the recognition of at least four major genotypes that infect a variety of mammalian species. Genotypes 1 and 2 HEVs are restricted to humans and transmitted *via* contaminated water in developing countries. Genotypes 3 and 4 HEVs have an extended host range including humans, pigs and other mammals and are responsible for sporadic cases of hepatitis E in both developing and industrialized countries.^{2,3} Genotype 3 HEV has a worldwide distribution whereas genotype 4 HEV is largely confined to Asia. Genotypes 3 and 4 HEV infections have been linked to the consumption of raw or undercooked meats such as pig liver sausages or game meats.^{24,25}

The full spectrum of species that are reservoirs of HEV is still unknown. Avian HEV from chickens and cutthroat trout virus from trout likely represent new genus.^{26,27} Recent studies have also characterized new HEV genotypes in rats in Germany,²⁸ bats worldwide,²⁹ wild boars in Japan,³⁰ and farmed rabbits in China.^{31,32} Further issues remain to be clarified, including whether rabbit HEV genotype differs from human and swine HEV genotype 3, whether HEV genotypes 1–4 can infect rabbits, and whether rabbit HEV can infect human and other animals. The aim of this review is to provide a look at the worldwide prevalence of serological and genetic markers of HEV in rabbits, the ability to cause cross species infection and the risk of zoonotic transmission of rabbit HEV strains.

2. Geographical distribution of rabbit hepatitis E virus

HEV was found in farmed rabbits in several geographic areas of China.^{31,32} A recent study also reported that farmed rabbits in the United States were infected.³³ Antibodies against HEV and HEV RNA were detected in various breeds of rabbits from 2 farms in Gansu province and in Beijing, China and 2 farms in Virginia, USA. The overall prevalence of antibodies against HEV in rabbits from the United States (36%) was lower than that in rabbits from Gansu and Beijing, China (57% and 55% respectively). By contrast, the prevalence of HEV RNA in serum and fecal samples in rabbits farms in the United States (16.5% and 15.3% respectively) was higher than that on farms in Gansu and Beijing, China (7.5% and 7.0% respectively). Neutralizing antibodies could play a role in this marker pattern.³⁴ Observed differences may be explained by the ages of the rabbits, due to variation in the duration of exposure. The difference may

also be explained by housing practices. In the US study, the prevalence of the antibodies was higher in rabbits caged in groups of 2–9 than in rabbits caged individually.³³ Because HEV is transmitted by the fecal–oral route, virus likely spreads easier between cage mates, thus increasing the numbers of HEV-positive rabbits.

A recent study has shown that rabbits in Europe were also naturally infected with HEV.³⁵ In France where cases of autochthonous hepatitis E are commonly reported,^{36,37} the prevalence of HEV in both farmed and population of wild rabbits was recently determined. HEV RNA was found in 7.0% of the farmed rabbits and in 23% of the wild rabbits. However, the ages of the rabbits – less than 3 months for farmed rabbits *versus* over 6 months for wild rabbits – and the tissues tested – bile for farmed rabbits and liver for wild rabbits – may explain the observed difference in HEV prevalence. Nevertheless, previous studies have shown that the virus loads in liver and bile samples from swine infected with HEV are similar.^{38,39} Although the greater prevalence of HEV in wild rabbit could be linked to their older age, a relationship between the prevalence of HEV in the various farms and warrens and rabbit age could not be tested for because their precise ages were unknown.

3. Experimental transmission of rabbit HEV

It has been shown that rabbits experimentally inoculated with the rabbit HEV seroconverted to HEV, shed virus in feces, became viremic and had serum liver enzyme elevation. Experimental inoculation of rabbits with human HEV genotype 4 showed seroconversion, viremia and fecal virus shedding in 2 of 9 rabbits and in none inoculated with genotype 1 human HEV.⁴⁰ This study indicates that rabbits could be a useful animal model for studying some aspects of rabbit HEV infection, although rabbits may likely be of a limited use as a model for studies of human HEV genotype 1.

Recently, Cossaboom et al. assessed the ability of rabbit HEV to cause cross-species infections in a pig model.⁴¹ They demonstrated that rabbit HEV strains from China and the United States were able to infect pigs when inoculated intravenously, as approximately half of the inoculated pigs developed transient viremia and sporadic fecal shedding. The infection of pigs by rabbit HEV was further verified by effective transmission of the virus recovered from pig feces to naive rabbits. Finally, it has been recently shown that rabbit HEV can replicate efficiently in human cell lines, PLC/PRF/5 and A549 cell lines.⁴² PLC/PRF/5 cells originating from human hepatocellular carcinoma and A549 cells derived from human lung cancer were previously shown to support efficient propagation of HEV strains not only from human but also from pigs and wild boars. All these data suggest that rabbit HEV may potentially cross the barrier species and infect humans. The identification of HEV receptor would also contribute to better understand the zoonotic transmission of HEV.

4. Antigenic and genetic studies

A recent study suggests that rabbit HEV is antigenically related to other HEV strains.⁴¹ A recombinant capsid protein of rabbit HEV showed cross reaction with antibodies raised against HEV strains from mammals such as rat, swine and human HEV, but also avian HEV. Conversely, it was shown that anti rabbit HEV antibodies cross reacted with capsid protein derived from human, swine, rat, and chicken HEV.

In the recent French study,³⁵ partial and complete nucleotide sequences of the HEV strains from rabbits were analyzed and compared with those of human HEV strains circulating in France to determine whether rabbits could be a reservoir for human infection. The genome organization of rabbit HEV is similar to those of other mammalian HEVs, with a 5' untranslated region,

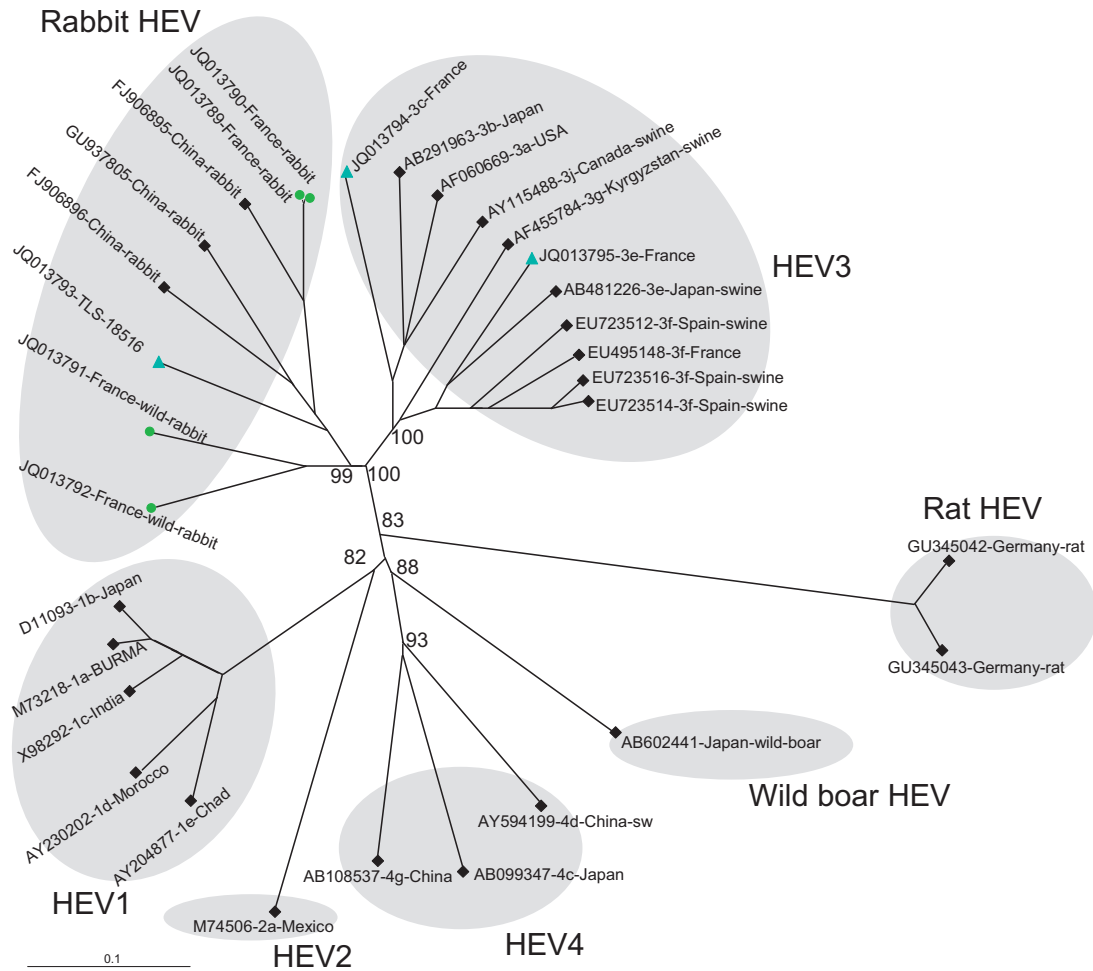


Fig. 1. Phylogenetic tree for the 1400-bp sequence of open reading frame 1 of the non-structural protein. Round: rabbit HEV. Triangle: human strains circulating in France. Diamond: reference strains. Genbank accession numbers are shown for each HEV strain. Scale bar indicates the nucleotide substitutions per site.

followed by ORF1, ORF2, ORF3 which partially overlaps ORF2 and the 3'UTR. ORF3 encodes a 113 amino acid protein, which has a length similar to genotype 3 HEV. Phylogenetic analyses based on ORF1 (≈ 1400 bp) (Fig. 1) and the full-length genome (Fig. 2) indicated that all the rabbit strains from China and France belonged to the same clade. One human strain, TLS-18516-human, clustered with the rabbit strains and appeared to be somewhat different from the 4 major mammalian HEV genotypes and the newly described HEV genotypes from rats and wild boar (Fig. 2). Although the full length sequences of the genomes of the rabbit strains and TLS-18516-human strain are more similar to that of genotype 3 HEV than to those of genotype 1, 2 and 4 HEVs, they do not seem to belong to the established HEV genotype 3 found in humans and swine, as recently suggested.^{30,43} Differences in the classification of rabbit HEV could be due to the full-length genomic sequences

used as the reference for phylogenetic analyses. Genotype 3 is very diverse, with 10 identified subtypes.⁴⁴ The analysis included the full-length genomes of subtypes 3f, 3c, and 3e, which account for approximately 74%, 13% and 5% of the human and swine HEV strains circulating in France.^{45,46} The other full-length genomes representative of genotype HEV subtypes were also included, but subtypes 3d, 3h, and 3i were not yet available in GenBank. The data indicated that the genomes of rabbit HEV or TLS-18516-human were less than 80% identical with genotype 3 HEV, whatever the method used to align the sequences (Table 1). This is compatible with the definition of a new genotype, as previously proposed.^{31,32}

A 93-nucleotide insertion in the X domain of the ORF1 of the human strain TLS-18516-human and of all the rabbit HEV strains was found³⁵ (Fig. 3). This insertion was also found in the rabbit HEV strains from China⁴⁷ and USA⁴⁸ and was not present

Table 1
Percent identities of full-length sequences among HEV strains from rabbits and HEV strains from humans.

Rabbit HEV strains	Human HEV strains, %identity				
	TLS-18516	HEV1	HEV2	HEV3	HEV4
GU937805 – China-rabbit	85.0	73.0–73.7	72.2	76.3–78.2	72.9–73.9
JQ013792 – France-rabbit	80.3	72.7–73.4	73.5	76.2–77.6	73.2–73.6
JQ013791 – France-rabbit	80.6	73.2–73.7	73.4	76.1–78.0	74.2–74.9

HEV1 (M73218-1a-Burma, D11093-1b-Japan, X98292-1c-India, AY204877-1e-Chad, AY230202-1d-Morocco); HEV2 (M774506-2a-Mexico); HEV3 (AF060669-3a-USA, AY115488-3j-Canada-Sw, AB291963-3b-Japan, TLS-TR19-3c, TLS-TR02-3e, AB481226-3e-Japan-Sw, EU495148-3f-France, AF455784-3g-Kyrgyzstan-Sw); HEV4 (AB099347-4c-Japan, AB108537-4g-China, AY594199-4d-China-Sw). JQ013791–JQ013792: W1-11 and W7-57-wild rabbits, respectively. Sw: swine.

5. Potential mechanisms of transmission to human

Similar to swine HEV in pigs, rabbit HEV is widespread in the rabbit population. So, like swine HEV,⁵² one can speculate that direct contact with infected rabbits, consumption of undercooked or raw rabbit meats and water contaminated by rabbit HEV may represent sources for human infections.

The contribution of rabbit HEV to the epidemiology of hepatitis E in humans is uncertain. HEV is endemic in southwest France and the annual incidence of locally acquired HEV infections has been estimated to be 3.2%.^{53,54} A case–control study found that the only factor independently associated with HEV infection was the consumption of game meat, mostly wild boar, deer, and wild rabbits.³⁶ However, molecular data from various studies carried out in France indicate that the majority of HEV strains identified belong to genotypes 3f, 3c or 3e that are prevalent in pigs and wild boar.^{36,45,55} A recent study indicated the same proportions of genotypes 3f, 3c, and 3e in the human and pig populations.⁴⁶ Although this could indicate that rabbit HEV is less readily transmitted to humans than HEV genotype 3, the primers used for PCR amplification were not specifically designed for rabbit HEV. Therefore, the true prevalence of HEV RNA in rabbits and humans may have been underestimated. In addition, it may have been difficult to genotype rabbit HEV because reference sequences have become available only recently.

6. Conclusion

In conclusion, farmed and wild rabbits can be infected with HEV. Phylogenetic analysis based on full length genomes and a molecular signature in the X domain of ORF1 both indicate that rabbit HEV could be a new genotype. The identification of a human HEV strain that is closely related to rabbit HEV strains and the ability of rabbit HEV to cause cross species infections in pigs reinforce the potential zoonotic risk of this virus. Further studies are needed to evaluate the contribution of the rabbit reservoir to human HEV infection and disease.

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Competing interest

None declared.

Ethical approval

Not required.

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