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Review

Zoonotic transmission of hepatitis E: Implications for public health worldwide

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Abstract

Since the year 1982, the Hepatitis E virus (HEV), enteric transmission, has been widely spread in many tropical and subtropical countries. HEV has multiple routes of transmission, such as food or water contaminated with faecal matter, person-to-person transmission or by the ingestion of raw or undercooked shellfish. It is important to consider the significance of zoonotic infections propagation, both in endemic areas as well as in developed countries, where there have been some sporadic cases. This article summarizes the research conducted to date, which supports the zoonotic transmission of HEV, its risks and how they are often underestimated.

Keywords: Human zoonosis; HEV; Public health

Virology and epidemiology

Hepatitis E virus (HEV) is transmitted primarily by the fecal-oral route. This is the most common route of transmission and widespread in developing countries where it can cause and has caused epidemics. Most of the well-recorded outbreaks of HEV have been caused by fecal contamination of drinking-water supplies. There are four strains of HEV which have been diagnosed in both humans and animals. Type 1 is the form of the HEV detected in humans in hyperendemic areas. The second strain, type 2, was found almost exclusively in human cases in Central America. Type 3 and 4 were recognized in humans and pigs in developed areas[1].

In addition, the concept of the disease in temperate and developed countries is changing. Conventionally known as pathology imported from endemic regions, usually by travellers from these regions, Hepatitis E is now being identified as an infection that may originate from animals and that has an incidence level much higher than it might appear from the number of symptomatic cases[1].

Disease burden: sporadic disease and outbreaks

Although little is known about the epidemiology of HEV in pigs, the characteristics of the disease identified in the Hepatitis E human cases, have led to greater classification of the strains as well as seroprevalence studies. This indicate a high level of anti-HEV seroprevalence in developing countries, as well as in some developed countries; for example in Korea it is present in the 50 % of pigs and in Canada in the 60 %[2]. Sporadic cases and outbreaks of HEV have been reported in Japan, United Kingdom, Netherlands, Italy, China, Israel, Germany and Vietnam, and have shown a close relationship between the virus genome present in pigs and the one that is produced in the human disease. Worldwide, the antibodies for HEV have been detected in a wide range of mammals including pigs, deer, monkeys, cattle, sheep, goats, dogs, rats and mice[3].

Factors such as having a wide host range and being able to replicate in the human gastrointestinal tract, as well as being stable, determine the probability that viruses may be transmissible via the zoo-

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notic food-borne route. The cases diagnosed in Japan, strongly support the theory that HEV could be transmitted as a zoonose through the consumption of raw or undercooked meats such as pork, wild boar venison or liver. In these occurrences of the disease, it was noted that 99.7 % of the nucleic acids were identical to those of the HEV found in wild boars and deer as well as those isolated from humans that had consumed the meat, suggesting that the virus infecting the animals was the same as that evident in the human form of disease[4].

An outbreak of acute hepatitis E focused around a Japanese family that had consumed raw deer meat about 3 weeks before. The sequence of the isolates found in the meat kept in the freezer and not consumed showed 100 % of coincidence with the obtained sequence of stool samples from the affected members of the family[5]. In addition, it was found that the seroprevalence of IgG antibodies anti-HEV was significantly higher in Japanese who had consumed raw deer meat compared to those who had not done so[6].

In an investigation in Japan[7] a man arrived to a hospital with acute hepatitis, 5 weeks later after eating liver of a wild boar not properly cooked. A person who had shared his meal was admitted to a hospital in the same city with fulminant hepatitis, where he subsequently died. Hepatitis E was diagnosed in both cases. In another investigation, 2 Japanese men from an association of elderly people, were diagnosed with acute hepatitis E, 39 days after consuming meat of wild boar badly cooked in at a barbecue. After serological tests, 11 out of the 12 men who attended the meal showed the presence of IgG antibody-HEV. In addition, 8 other men had signs of having suffered an acute infection of HEV detected 6 months after consuming this type of meat. None of them had recently traveled to a hyperendemic area of HEV. The genome sequence of HEV amplified and retrieved from the blood of the 2 original patients showed a 99.4 % of homology between them and 92 % homology with other sequences of genotype-3 HEV originated in Japan[8].

A more recent study reported that 9 out of 10 patients, suffering from acute or fulminating hepatitis E, had consumed badly cooked pork, 2 to 8 weeks before the onset of the symptoms. A follow up survey of meat retail sales, revealed that 1.9 % of raw pork liver was contaminated with HEV[9]. In addition, a strain of HEV isolated in wild boar in Japan had a 99.7 % homology with a variant of HEV detected in a wild deer from the same forest, and also with a strain isolated from humans that consumed the deer meat and developed symptoms of hepatitis E[4]. In China, Japan, United Kingdom and the Netherlands, genomic sequences of HEV from indigenous cases of human hepatitis E have shown great similarities to those of the HEV evident in pigs[10].

Zoonotic HEV transmission via food

Transmission via food is an opportunity for an unlikely transmission event to occur relatively easily. Zoonoses with a fecal-oral route of infection are examples of this. For instance HEV types 3 and 4 are probably transmitted from pigs to humans. The presence of antibodies and RNA HEV in pigs in Nepal[11] was detected in 1995 and, in 1997 the genomic sequence was published, indicating that the pig virus was closely related to the human[12]. Shortly after in the United States, two strains of human HEV showed almost identical sequences to that pig strain[13]. This data suggests a very close relationship between human HEV and pig[14].

In the United Kingdom, the current HEV prevalence in pigs is approximately 80 %, and has remained this level since the beginning of 1990[15,16]. On the other hand, veterinarians and caregivers of land pigs showed a prevalence 1.5 times higher of these antibodies compared to those from the voluntary blood donors, which strongly supports the theory of a possible zoonotic transmission pattern[17]. Studies in South America have detected the anti-HEV in pigs bred for human consumption, as in Brazil, for example, where seroprevalence of the antibodies was between 63 % and 95 %[18]. On the other hand, in Buenos Aires, Argentina, infected pigs have been identified with HEV suggesting that pork may be a transmission channel for this infection. Upon isolation of the virus it was found to belong to the genotype-3 and closely related to a strain of HEV identified in Austria implying a possible European origin of this infection[19].

In Argentina the HEV study is not usually included for the diagnosis of fatal hepatitis and a 30 % of this disease is unknown in its etiology. To explore whether HEV could be the cause for fatal hepatitis in Argentina, serum and/or fecal samples of 35 children (average age 6 years) were analyzed. The RNA HEV was found in 3 children: 2 boys of 12 years old residents of Buenos Aires suburbs and a 3 years old girl from Corrientes. The HEV strains

found were genotype 3, closely related to the strains found previously in sporadic cases in humans and pigs in Argentina[20].

Evidence of zoonotic transmission

In our opinion, due to the great homology between the strains of humans and pigs HEV[13] with up to a 97 % genetic identity in the encoded proteins, pigs should be considered the main natural reservoir for the infection. Pigs act as potential reservoirs of HEV in hyperendemic or endemic areas. Under experimental conditions, HEV human has been transmitted to sheep[21].

HEV's transmission by animals is supported by the following facts:

(1) The discovery of a seroprevalence rate for anti-HEV is 20 %-25 % among veterinarians in the United States[22], and 10 % of the people who work with pigs[23];

(2) In countries with high endemicity for HEV (anti-HEV 20 % in apparently healthy human population) a prevalence of 72 % was detected in pigs[24];

(3) Studies that have detected antibodies against the HEV in pigs in developing countries such as Nepal[25,26] and Thailand[27], and in industrialized countries like Canada, Korea[28], Taiwan[29], Australia[30] and New Zealand[31]. Anti-HEV was also detected in other animals like rats[32-34], dogs, sheep, goats and cows[2, 35]. These data of HEV seroprevalence suggest that certain animal species are exposed to the virus (or a related agent) but epidemiological details for the cause of the infection are yet to be known. The genomic genetic variability of human HEV could be caused because the virus is originated in animals. An hypothesis would be that both domestic and farm animals, have their own genotype variants of HEV. As a result, given that all the viruses are specie-specific, each strain of HEV is enzootic for every animal species, within the same geographical area;

(4) Several studies have been published showing a high prevalence of anti-HEV in people who have had an occupational exposure with pigs. In a survey conducted in eight states of the United States, 20 % to 25 % of pig's veterinarians proved to be anti-HEV[17]. The use of animal's organs and tissue for xenotransplantation might be a problem, if the transmission from pigs to humans is confirmed, and it should be seen as an agent with xenogeneic potential[36].

Animal reservoirs of HEV

Occasionally, hepatitis virus in animal's DNA may infect humans through direct contact causing sporadic cases of acute hepatitis E, however, incapable of causing epidemics. This is because animal's HEV viruses are not fully adapted to human's replication, as there are several endemic or epidemic variants which can indeed cause large outbreaks. If this hypothesis is correct, the geographical areas and animal species, will determine the genotype present in the sporadic cases of acute hepatitis E. It would be important to check if there are fundamental differences in men's susceptibility, when comparing the variants of human HEV circulating in epidemics or endemics and enzootic strains of animal origin that might have been exposed.

Studies of infectivity in pigs and macaques have confirmed cross infection between pig's and human's HEV[37] in developed countries, both strains are grouped phylogenetically. The pigs were inoculated with the isolated human HEV and the virus was subsequently found to be present in the blood (viremic). Soon after, the animals quickly became seroconverted. This suggests that the variant was perfectly suited to the pig and so it might be its true origin. Primates have also been known to become infected with the strain found in pigs and lambs and rats with the human form.

The consumption of water, contaminated with faecal matter, has given rise to major epidemics of HEV, while the ingestion of raw and undercooked shellfish has been the source of sporadic cases in endemic areas. However, there is also another possibility of zoonotic virus transmission to humans: after consumption of meats such as pork and wild boar carrying the virus, for which there have been many documented cases. Further evidence for possible HEV transmission between humans and pigs comes from studies in Taiwan, showing that the subgenomic sequences of HEV obtained from pigs and humans form a monophyletic group[38, 39]. Several other studies have also shown that it is possible for HEV to cross the interspecies barrier which raises major concerns to Public Health. Therefore anyone who works or comes into contact with pigs has a higher risk of infection by HEV.

HEV, similary to Hepatitis A virus, has always been identified as a disease with an epidemiological pattern linked to the consumption of contaminated

food and water, more commonly found in areas with deficient social conditions. The introduction of molecular biology techniques provided the evidence needed to show that in developed countries the infection by HEV is not uncommon, it has indigenous character and a different epidemiological pattern related to the consumption of animal products, such as pork[40].

Viral evolution and its relevance for zoonotic transmission of HEV from animals to human beings

The viruses are elementary biosystems with a minor ability to replicate in nature. They are grouped into 60 families, depending on its structure and genomic organization. But, only about 20 families infect human-primates. Non-human primates are the mammals closest to man. Zoonoses are diseases that can be transmitted from both wild and domestic animals to humans and are public health threats worldwide. Nonetheless, several examples demonstrate that the virus is also capable of spreading from animals to humans. For instance, avian influenza's virus (H5N1) that affects humans in close contact with sick or dead birds and similarly, the simian foamy viruses (SFV), has been known to infect the visitors of the "temple of Monkeys" in Bali, Indonesia[9].

Moreover, it is well known that RNA virus has an evolution rate much greater than DNA virus in the infected host. This creates a different adaptation between the times of their host and the times of evolution of the new RNA virus. Though, co-evolution phenomena between RNA virus and its mammal hosts have been described. This, in itself is a contradiction as, according to the estimates of evolutionary history. The RNA virus would have emerged long after the adaptation of their hosts. Evolutionary models do not yet provide a clear answer for this contradiction. There is a case, however, seen in the co-evolution between RNA virus (the SFV mentioned above) and its various primate hosts, where it showed that the evolution rate was exceptionally low for the RNA virus, temporarily matching stages of viral diversification with those of primate adaptation[24].

It was demonstrated that some animals, including pigs, also constitute a major reservoir for zoonotic diseases such as HEV, either by the accidental transmission of the virus from a non-human host to a human, as for the emergence of new viruses, by means of inter species exchange. Further research is therefore imperative in order to help quantify the risks associated with the transmission pig and human HEV. Such studies would help reduce the risk of exposure by reducing the chances of infection.

Assuming that the HEV virus contracted in developed countries of the first world behaves as a zoonose makes a difference as it allows increased conceptual thinking, allowing for the infection to be viewed and examined from a different perspective, taking into account new elements such as the role of animals as reservoirs and potential transmitters of the virus. The detection of a zoonotic carrier in animals closely in contact to the man, especially pigs, precisely defines the importance of the epidemiology of the disease. Increasing progress in molecular technologies has allowed us to phylogenetically characterize the genotypes of isolated strains, allowing for facilitated comparison of the viruses according to their geographical origin and the host in which they were located.

Using this method the strains can be viewed and geographically grouped, regardless of the type of mammal in which they were found. For example, the strains of HEV isolated in the United States are very similar to each other, aside from having been isolated in both humans and pigs. What's even more interesting is that there is in fact a greater number of strains isolated in humans than in pigs[41]. These findings confirm the importance of studying the virus in non-human mammals, to thus illustrate the zoonotic transmission of the pathogens to those closest to man. This has been and remains an important public health issue and it presents a dangerous risk for the acquisition of new diseases. These risks could indeed be reduced through health education campaigns. This type of information would equally help the public to understand the origin of many viruses that infect humans. The analysis of the viral infections behavior in non-human hosts would also help us to discover more molecular and immunological information which would aid us in fighting these diseases. The use of non-human primates as animal models for experimentation has been invaluable for the study of the pathogenesis of viral diseases and for the development of new drugs and vaccines for multiple viruses, such as polio, yellow fever, hepatitis B and C, and more recently HIV; although, however, it is important to note that these animal models never reflect exactly what happens to humans.

Discussion

Many of the emerging infectious diseases, including HEV, are zoonoses. Since a zoonose can infect both

animals and humans, the medical and veterinary communities should work closely together in clinical, public health, and research fields. In the same way physicians, veterinarians and comparative medicine research teams should also be encouraged to study zoonotic agent-host interactions. These initiatives would increase our understanding of how zoonose expand their host range and would, ultimately improve prevention and control strategies. Risk-benefit ratios for ongoing animal exposure could be weighed up and discussed by both veterinarians and physicians as veterinary input might be helpful in difficult decisions. Furthermore, joint medical and veterinary workshops on zoonotic risks to human health could help forge ties and facilitate opportunities to establish these types of collaborative efforts.

Two final considerations, first, to study the viral infections in non-human primates is of paramount importance for both the preservation of biodiversity, as for the prevention of great impact epidemics on human health. Second, it is also important to analyse the health risks to which they are exposed as many of these animals are already in danger of extinction.

So far the number of recognized zoonotic foodborne viral infections is very limited, and to date it is not clear if this is due to much underreporting or to the fact that these infections actually do happen only rarely. Whether this mode of transmission plays a role in the epidemiology of HEV remains to be seen. Furthermore, in the interest of health, the possibility of the virus crossing the species border implies that we must recognise the hepatitis E virus as a zoonose. In the coming years it will be necessary to carry out in depth studies about the adaptive capacity of the virus in humans and its transmissibility potential from an animal reservoir[42]. Prevention measures should not be limited to an increase in the sanitary controls of water and will have to establish specific actions on the animal reservoir. A vaccination could be an effective measure in the control of this disease but pilot tests would be necessary in order for the active immunisation to be successful[43].

Few may argue that food-borne viruses are unimportant. We consider, however, that these are not a minor issue. Since zoonoses are animal diseases that can infect humans, public health officials need to work more closely together to control, prevent, and understand them. In the individual health setting, collaborative input from both veterinarians and physicians would help assess a patient's potential zoonotic disease risks due to animal exposure[44].

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