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REVIEW

Hepatitis E Virus: A review of the current status and perspectives

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Abstract

Hepatitis E virus produces approximately 20-million infections per year; symptomatic cases are over 3-million and deaths are approximately 60,000. Generally, it is self-limited; however, it can cause up to 30% mortality in pregnant women and can be chronic in immunosuppressed people. The transmission path of the Hepatitis E virus is principally fecal-oral, especially in developing countries; in industrialized countries, it is transmitted as a zoonosis, through organ transplants or blood transfusions. The vaccine developed is only licensed in China. Currently, no treatment is available for the HEV infection and work is underway in identifying the viral cycle and the immune response. This article sought to offer a review of the theme on the hepatitis E virus, from the last six years, to describe current general aspects of the Hepatitis E virus, genome, ways of transmission and contribute to its visibility for its prevention and control.

Key words: Hepatitis, virus, infection.

Virus de la Hepatitis E; revisión del estado actual y perspectivas

Resumen

El virus de la hepatitis E produce aproximadamente 20 millones de infecciones por año; los casos sintomáticos superan los 3 millones y las muertes son aproximadamente 60.000. Generalmente es autolimitada; sin embargo, puede causar hasta un 30% de mortalidad en mujeres embarazadas y puede ser crónica en personas inmunodeprimidas. La vía de transmisión del virus de la hepatitis E, es principalmente fecal-oral; especialmente en los países en desarrollo. En los países industrializados, se transmite como zoonosis, a través de trasplantes de órganos o transfusiones sanguíneas. La vacuna desarrollada solo tiene licencia en China. Actualmente, no hay tratamiento disponible para la infección por HEV y se está trabajando para identificar el ciclo viral y la respuesta inmune. Este artículo buscó ofrecer una revisión del tema sobre el virus de la hepatitis E, de los últimos seis años, para describir aspectos del virus de la Hepatitis E, genoma, vías de transmisión y contribuir a su visibilidad para su prevención y control.

Introduction

The hepatitis E virus (HEV) is currently a public health problem, both in developed and developing countries[1]. Said virus is considered an emerging zoonotic pathogen and one of the principal causes of acute viral hepatitis throughout the world; with a high risk of developing chronic infection in immunosuppressed patients. However, the global burden of the HEV infection has not been evaluated exhaustively [2]. Since ancient times, registries are available of outbreaks of viral hepatitis globally. In Latin America, it is considered that, due to this health event, high mortality occurred in the pre-Hispanic population, in the territory now known as Central America[3].

Although this virus generates a high disease burden globally, in Colombia it is still not deemed a public health problem[4]; being the most-common cause of acute viral hepatitis in the world, without direct-acting antiviral treatment available. According to a recent WHO report, 20-million people are infected with HEV annually, resulting in 44,000 deaths[1].

In 1955 in Delhi, India, an HEV epidemic was reported with approximately 29,000 cases[5]; thereafter, outbreaks of hydric origin continued to be reported and cases in great numbers were reported as non-A and non-B, which is why this disease was denominated as enteric non-A non-B hepatitis (ENANBH). Later, by late 1978, another epidemic outbreak was again reported also of hydric origin in the Kashmir valley with 52,000 cases and 1,700 deaths; the symptomatology was similar to that of hepatitis A and negative for hepatitis A and hepatitis B, confirming them as ENANBH[6]. In 1981, a Soviet military camp in Afghanistan had a hepatitis outbreak; for its study, a volunteer ingested a concentrate of feces samples from infected soldiers, causing him acute hepatitis. The

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serum from the volunteer was negative for the hepatitis A virus (HAV) and hepatitis B virus (HBV), which suggested a new pathogen responsible for this infection [7]. This article aims to offer a review of the topic on the hepatitis E virus, from the last six years, to describe current general aspects of the hepatitis E virus, its genome, currently identified transmission routes, and thus contribute to its visibility, for its prevention and control.

Hepatitis E virus

The HEV is formed by an icosahedral particle without envelope of about 32 nm; withstands the acidic and alkaline conditions of the intestinal tract, facilitating the fecal-oral transmission path.

The HEV is a positive-strand, class IV RNA virus belonging to the genus Hepevirus, only member of the family Hepeviridae[8].

This family is made up of the genera: Orthohepevirus that infects terrestrial vertebrates and Piscihepevirus, which infects fish. The Orthohepevirus is comprised of four species, A – D, with different host types. The genus Orthohepevirus *A* has the HEV variants that infect humans. China, between 1986 and 1988, had a great epidemic affecting 120,000 people and the genotype identified was described as genotype 1, which can be found in Asia, Africa, and South America. In Mexico, during an outbreak between 1986 and 1987, genotype 2 was detected, although it can also be found in Nigeria and Chad. These two genotypes are related and restricted to humans; their transmission is related with deficient sanitation and contaminated water, only in humans[9,10].

Genotypes 3 and 4 were identified in 1995 and 2003, respectively. The HEV genotype 3 is disseminated globally and is prevalent in industrialized countries. The HEV genotype 4 is limited to east Asia, including Japan, China, and South Korea; its reservoir includes pigs, boars, deer, and rabbits, it circulates among humans, pigs, rabbits, deer, and mongooses; VHE4, identified in humans and pigs[8,9]. In many parts of China, the HEV genotype 4 (HEV-4) has emerged as the most-common genotype that causes acute hepatitis. Recently, it was shown to cause persistent infections in transplant receptors[11,12,13].

The HEV5 and HEV6 represent strains identified in boars from Japan, where unique nucleotide sequences were found previously designated as HEV of genotype 5 and genotype 6; however, it is important to bear in mind that not all boar HEV isolates belong to genotypes 5 and 6; most of the HEV isolates from boar are classified as genotypes 3 and 4 with zoonotic capacity[14] (Table 1).

In 2014, HEV was reported in camelids and dromedaries from Dubai and then, in 2016, in Bactrian camels from Xinjiang (China); in the genomes of samples obtained from these camels, nucleotide differences were found > 20% compared with the complete HEV genomic sequences available. For this reason, two new genotypes were proposed: HEV-7 for dromedary camel (DcHEV) and HEV-8 for Bactrian camel (BcHEV). A case of chronic HEV-7 infection in a liver transplant receptor, frequent consumer of camel products, indicates the zoonotic potential of these new genotype[15].

Genomic organization

The HEV has a diameter from 27 to 34 nm and a genome consisting of three open reading frames (ORF). The 5' non-translated region (NTR) (27 nucleotides) is covered with a 7-methylguanine and is followed by ORF1, which encodes the non-structural proteins (NS) necessary for replication. The ORF2 encodes the central protein of the viral capsid, while ORF3 partially overlaps ORF1 and encodes a protein like viroporin. This virus' genome hosts a 3' NTR (65 nucleotides) that ends with una poly (A) tail (Figure 1.)[16,17].

Table 1. Genotypes of the hepatitis virus, hosts, and transmission paths.

Genotype 1. Sub genotypes a-e.	Genotype 2. Sub genotypes a, b	Genotype 3. Sub genotypes a , j	Genotype 4. Sub genotypes a, g	Genotypes 5, 6.	Genotypes 7.8
Identified between 1986 and 1988	Identified between 1986 and 1987	Identified in 1995.	Identified in 2003	Identified in 2013	In 2014, reported camelid and dromedary in 2016
Isolated from sample of human origin. is found in developing countries in Asia and Africa.	Isolated from sample of human origin. Identified during a hepatitis E outbreak in Mexico.	Isolated from sample of human serum origin	Isolated from sample of human and animal origin	Isolated from wild boar samples in Japan	Isolated from camels in the Middle East and Chinese
Natural host: restricted to humans	Natural host: restricted to humans	Hostesses: human, pig, wild boar, deer	Hostesses: human, pig, wild boar, deer	Natural host: wild boars thus far	Natural host: camels in the Middle East and Chinese
It is transmitted from human to human by contaminated water. Fecal-oral route	It is transmitted from human to human by contaminated water. Fecal-oral route	Zoonotic transmission route (consumption of poorly cooked meats). organ transplantation and blood transfusions	Zoonotic transmission route (consumption of poorly cooked meats). organ transplantation and blood transfusions	Strains obtained from wild boars in Japan	Zoonotic transmission route consumption of meat and milk. Organ transplant.
Predominant in the developing countries	Predominant in the developing countries	Predominant in industrialized countries	Predominant in industrialized countries	Recently identified in Japan	Detected in United Arab Emirates

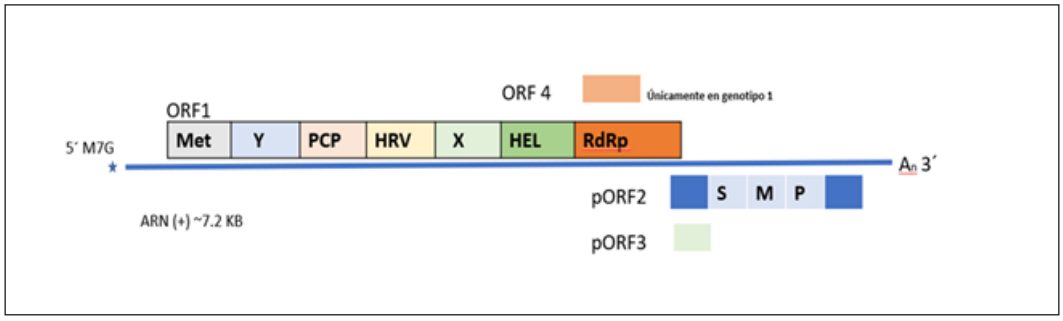

Figure 1. Genomic structure of the hepatitis E virus. (Modified from Nimgaonkar et al., 2018[6]
Hepatitis E virus (HEV) is a positive polarity single stranded RNA of approximately 7.2kb; with consisting of three open reading frames: ORF1, ORF2 ORF3; once it has entered the cell and the viral capsid is eliminated, it is translated by the host's ribosomes in order to produce the poly protein ORF1, which forms the non-structural region of the virus and allows its replication. Only in HEV genotype 1 is it associated with ORF1 ORF4, which is believed to enhance the activity of RdRp, which is a non-structural protein that is part of ORF1, when translated into a protein. This is initially transcribed to a negative polarity strand as a template for the production of new virions and also transcribes into a shorter subgenomic ARN that contains ORF2 and ORF3. ORF2 is translated into capsid protein (pORF2) and ORF3 protein (pORF3), a viroporin, which is required for virion exit[17].

These reading frames have different sizes and functions; ORF1 is the largest viral gene, encodes for a non-structural polyprotein of 1,690 amino acids that permit viral replication of the genome. It encodes the non-structural proteins of the virus, including the RNA-dependent RNA polymerase (RdRp), RNA helicase, and methyltransferase, it contains other domains with little characterization, such as the "X" domain and the "Y" domain, the hypervariable region (HVR) and a cysteine protease like papain (PCP)[6].

The ORF2 encodes the preORF2 structural subunit and corresponds to the viral capsid protein, being the virion's main structural component; this protein is highly immunogenic. The production of the currently available vaccine has focused on this protein and uses the ORF2 gene from a genotype 1 strain[18]. The ORF2 has 1,983 nucleotides, starts at nucleotide 37 downstream of the ORF1 stop Codon and overlaps on the nucleotides of ORF3[19]. Recently, it was demonstrated that the HEV produces three different forms of ORF2: the first form is described as ORF2i, component of infectious particles; the second is secreted ORF2g (ORF2 glycosylated); and the third is ORF2c (ORF2 split off) that is not associated with infectious particles but found as antigen in serum of infected patients[20].

The ORF3 is the smallest of the entire genome, with functions yet unknown; it is translated from a sub-genomic RNA that makes up a protein of approximately 115 amino acids. It has been found in viral particles present in serum from patients and in cell cultures; it is necessary for the release of the viral particles[21,17].

The ORF4 was recently identified as a new reading frame that is fully embedded within ORF1, exclusively in genotype-1 strains. The transitory expression of ORF4 produces a protein of molecular weight of 20 kDa; this ORF4 protein interacts with the RdRp, helicase and X viral proteins, stimulating viral RdRp activity and reinforcing viral replication[22,19].

The HEV was denominated "quasi-enveloped" in 2016, found in enveloped and not enveloped forms. It is eliminated in feces as a non-enveloped virus, but HEV taken to cell culture has a lipid cover. This form of appearing "quasi-enveloped" with lipid cover, in the blood circulation, confers it protection against neutralizing antibodies against the ORF2 protein (capsid protein) and the ORF3 protein, which allows it to evade the humoral immune response[6]. Although both viral forms are infectious, the non-enveloped virus is 10 times more infectious than the quasi-enveloped form[16].

HEV replication

Systems to cultivate HEV *in vitro* have been developed only recently, and the viral replication mechanism continues being hypothetical. Analysis of the genome has been performed and, through analogies with other known viruses, the HEV replication cycle has been proposed[23].

On the HEV's mechanism of entry to the cell, little is known and the receptor is still unknown, but it has been shown that host factors are involved in the entry into the cell of naked HEVs, such as heparan sulfate proteoglycan, which participate in the cellular binding of many enveloped and not enveloped viruses and, in this case, to human hepatoma cells; GRP78, also known as binding immunoglobulin protein (BiP) molecular chaperone in the endoplasmic reticulum also involved in the entry of the virus into the cell. Asialoglycoprotein (ASGP) are galactose receptors found principally on the surface of hepatocytes and ATP5B (5β subunit of ATP synthase) that, although it is a mitochondrial protein, a fraction is expressed on the cell surface and is implicated in viral infections [24]. Binding to the cell surface and entry to the host cell are the initial and basic moments in the cycle of viral infection. The expression of specific membrane components that allow viral attachment to susceptible host cells is determined by viral tropism in the target cell[25].

The hepatitis E virus can present itself as a non-enveloped virus, where the capsid cover interacts with the surrounding environment, or as a quasi-enveloped virus (eHEV), where the capsid is coated with an exosome membrane; both forms are infectious, however, it is considered that the non-enveloped virus is a much more infectious form than the quasi-enveloped presentation[26].

The HEV and eHEV use different mechanisms to enter the cell. The entry of eHEV is believed to depend on the degradation of its membrane in the lysosome[27].

For eHEV, the virus enters the cell through clathrin-dependent and dynamin-dependent receptor-mediated endocytosis, a GTPase that mediates membrane fission during endocytosis and enables degradation of lysosomes coat lipids[6,28]. After endocytosis, the viral genome is released in the cytoplasm and the positive sense HEV RNA is translated by host factors into the ORF1 polyprotein from ORF1, which contains the RNA-dependent RNA polymerase (RdRp); the RdRp then transcribes full-length negative sense complementary viral RNA, which serves as a template for full transcription of positive sense RNA and a 2.2-kb subgenomic RNA[29]. When this sub genomic RNA is translated, the ORF2 and ORF3 proteins are produced. Thereafter, upon continuing, the cycle produces the viral assembly and the release of the new virions. During this process, the HEV virion can be released as a "quasi-enveloped" virion (eHEV) in exosome membranes toward the blood stream or pass with its lipid cover through the bile duct, where it degrades and is released in its "naked" form in the stool. When the released eHEV enters the blood stream, its quasi-enveloped form protects it neutralizing antibodies against pORF2 and pORF3 (Figure 2).

Extrahepatic replication

The target cell of HEV par excellence is the hepatocyte; however, extrahepatic replication of the virus has been demonstrated. Among the extrahepatic manifestations associated with the infection due to HEV, there are neurological manifestations, like the Guillain-Barré syndrome, neuralgic amyotrophy, encephalitis, myelitis, myositis, vestibular neuritis, peripheral neuropathy, Bell's palsy and multiple mononeuritis, aplastic anemia, acute thyroiditis glomerulonephritis at the renal level, manifesting as proliferative membranous glomerulonephritis and cryoglobulinemia; anemia and acu-

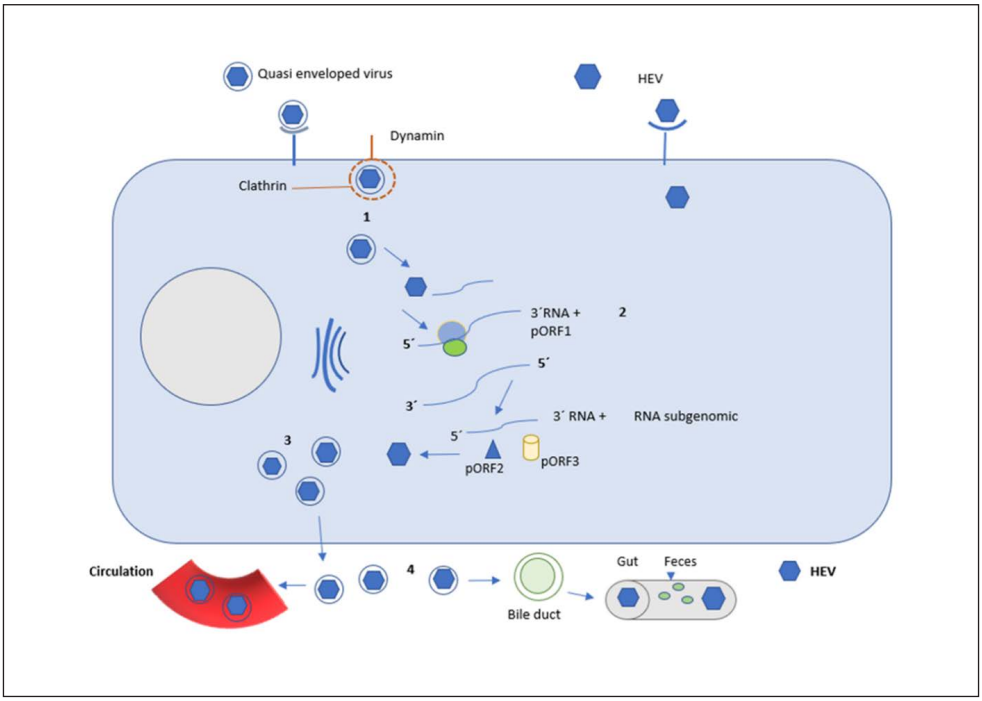

Figure 2. Schematic representation of the HEV replication.
The non-enveloped virus has a more efficient replication and a mechanism of entry to the cell different from that of the enveloped virus[6]; for the quasi-enveloped virus, the replication cycle is described in the following manner: 1: the cycle starts with entry of the viral particle onto the cell through endocytosis by using a clathrin- and dynamin-dependent receptor; upon entering the cell, the lipid cover is degraded by lysosomes and leaves mRNA exposed, the polyprotein ORF1 (pORF1) is translated into a single RNA of positive polarity and then transcribed into an RNA of negative polarity with its full length; 2: negative-polarity RNA allows positive-polarity RNA to be transcribed to generate virions and a subgenomic, shorter RNA containing the capsid protein ORF2 (pORF2) and the protein ORF3 (pORF3) a viroporin essential for viral release. 3. Subsequently, there is the assembly of the capsid and covering of the virion with the lipid membrane (possibly derived from the trans-Golgi network bound for the cell surface). 4: viruses are released and take two routes, one goes into the bloodstream as eHEV, where the envelope protects it from being neutralized by antibodies to pORF2 and pORF3, it is also considered that this form is less efficient to infect the cell; the other route is to enter the bile duct, where the lipid envelope is degraded and released in the feces.

te pancreatitis; however, the pathogenesis of these events is unknown and further studies are necessary to permit defining these associations[30].

Clinical aspects of the hepatitis E infection

Outbreaks of hepatitis E are a serious public health problem in developing countries. The disease causes acute infections, principally in young adults. The mortality rate is approximately 2%; however, it can exceed 20% in pregnant women in some regions of India[31].

The HEV infection is usually asymptomatic, jaundice occurs in 5% to 30% of infected patients [26]. The prodromal phase with its nonspecific symptomatology, which includes fever, nausea, vomits, and anorexia, can last up to one week. Symptoms tend to resolve spontaneously after a few days to a week. However, in the presentation of outbreaks, the mortality rate varies from 0.5% to 4.0%[32].

Despite starting as an asymptomatic event most of the times, there are reports of progression of the infection to the chronic form with hepatic damage and cirrhosis, especially in immunosuppressed patients, solid organ transplant receptors, carriers of the human immunodeficiency virus (HIV) and people with hematologic malignancies[33]. During gestation, studies have demonstrated that especially during the second and third trimesters, there is greater affectation; the third trimester is the stage during which 30% of maternal mortality occurs. The HEV infection during pregnancy is also associated with high incidence of premature births and vertical transmission, as well as other complications, like disseminated intravascular coagulation[34].

Epidemiological behavior

Infection due to the hepatitis E virus (HEV) is a cause of viral hepatitis of global distribution; it is hyperendemic in tropical regions, causing outbreaks in these countries, especially after great floods or in refugee camps. It is estimated that the number of symptomatic infections due to HEV in tropical countries is above 3 million per year[35]. The global burden of hepatitis E reports approximately 20-million cases annually of which 3.3-million cases are symptomatic and 60,000 deaths are attributed to HEV genotypes 1 and 2[6].

The first well-documented hepatitis E epidemic took place in India between 1955 and 1956, affecting 29,000 people. It was determined that the cause was due to the contamination of water sources. The epidemiological patterns vary according to the region where hepatitis E is endemic if compared with those that are not; in endemic areas, epidemics are more frequent. This behavior has been observed in China, India, Asia, the Middle East, and Africa[36].

It has been found that genotypes 1 and 2 are the principal causes of epidemic acute hepatitis and endemic in developing countries. Under poor hygienic conditions, these genotypes are transmitted among humans via fecal-oral means and via contaminated water. However, in developed countries, genotypes 3 and 4 are of zoonotic origin, with transmission through foods and through contact with the infected animal. It is possible for transmission through blood transfusions and organ transplants[37]. It is a particularly severe disease when it occurs during pregnancy[38] (Table 2).

Immune response

The immune response during acute hepatitis has been studied in both infected volunteers and non-human primates; findings suggest an incubation period of approximately 4 to 6 weeks since the infection until the onset of symptoms. Viremia during infection due to HEV persist for approximately one month after the symptoms appear in healthy individuals; viral RNA in feces has been detected in studies with patients since the first week after the start of the disease up to 28 days later and in serum from the same patients, since the first until the sixth week. Immunoglobulin IgM anti-HEV was detected on the first week after the symptoms appeared and diminished during the following six weeks[46].

Seroconversion against the hepatitis E virus was demonstrated by a volunteer who ingested a feces mixture contaminated with ENANBH; said volunteer developed antibodies during the early phase of the disease and using his serum it was possible to visualize spherical virus particles of approximately 27 to 30 nm in fecal samples. With these same particles, the same particles were visualized in samples of cases documented in Asia, Africa, and North America, leaving evidence that the HEV in the different regions of the world were related[47].

The mechanism of HEV immunopathogenesis remains difficult to identify. The innate immune response forms the first line of defense against viral infections, including HEV. The retinoic acid inducible gene I (RIG-I) detects pathogen-associated motif patterns (PAMP) in viral RNA to induce innate antiviral immune responses. It has been shown that the RIG-I path plays an important role during the HEV infection. However, the RNA-HEV motifs recognized by RIG-I are still unknown[48].

Type I interferon (IFN) is also in the first line of defense and once the cell is infected, the virus genome is recognized by pathogen recognition receptors and induces activation of intracellular signaling cascades. It has been found that some of the genes encoded for HEV have the capacity to interrupt the signaling cascades for antiviral immune responses and do not permit production of cytokines / chemokines. Currently, the HEV evasion mechanisms are being studied[49].

Pathogenesis of hepatitis E

The hepatitis E virus is an important human pathogen that causes acute and chronic infection. Currently, the replication and pathogenesis mechanisms are not well known[50].

Table 2. Epidemiological behavior of the hepatitis E virus

Country	Date	Genotype	Source of infection	Transmission path	Population at risk	Behavior
India	1955 – 1956 The first well-documented hepatitis E epidemic.	1 Asian strains	Contamination of water sources. poor hygienic conditions	Transmitted between humans fecal-oral path	Humans. Responsible for severe hepatitis in pregnant patients and infants [39]	Are the principal causes of epidemic acute hepatitis and endemic in developing countries. Epidemic China, India, Asia, Oriente Medio y África. Are found exclusively in humans. Considered endemic in some regions of Asia and Africa; was also detected in Cuba and Venezuela. Uruguay autochthonous HEV.
Mexico	1980s, Outbreak in the where HEV-Gt2 was Identified [40]	2 A single Mexican strain	Contamination of water sources. poor hygienic conditions		Humans. Responsible for severe hepatitis in pregnant patients and infants	Are found exclusively in humans. Mexico and Africa
USA	1997. From the first known case of HEV in an individual who had not recently travelled outside the continental US [41]	3 (HEV US-1)	Zoonotic origin, have been found in humans and animals such as pigs, boars, and deer	Transmission through foods and through contact with the infected animal. It is possible for transmission through blood transfusions and organ transplants	older people, immunocompromised individuals, patients with chronic liver diseases, workers contact with HEV-infected animals	Is the most prevalent genotype in Europe. Sporadic cases in industrialized countries.
China	1999 Human HEV strain obtained from Chinese HEV patients [42].	4	Zoonotic origin, have been found in humans and animals such as pigs, boars, and deer		older people, immunocompromised individuals, patients with chronic liver diseases, workers contact with HEV-infected animals	Sporadic cases in China, Japan, and Taiwan
Japan	2014 Japan[43]	5-6	Wild boars	Possibility of zoonotic infection	humans	the pathogenicity, epidemiology, remain unclear
Dubai	2014, reported dromedary [44]	7	Dromedary camel	consumption of camel products	humans	unknown
Xinjiang (China)	2016 reported Bactrian camels[45]	8	Bactrian camel	consumption of camel products	humans	epidemiology, zoonotic potential, and pathogenicity of the virus were unknown

It is still not clear how through fecal-oral transmission, the virus particles reach the liver. Recent research has indicated that, in primary cultures of intestinal cells, RNA-HEV and ORF2 antigen were detected in the intestinal crypts of a patient with chronic infection. This information suggests that, upon replicating in the intestinal tract, it circulates in quasi-enveloped form; reaches the liver through blood circulation and there it replicates in hepatocytes, the virus is released and through circulation it returns as a quasi-enveloped virus or without the lipid cover that is eliminated by the bile salts and, thus, is liberated in the feces. Bearing in mind that the HEV does not produce cytopathic effect, liver damage may be due to cytotoxic T lymphocytes and natural killer cells[51].

In immunocompetent individuals, most infections due to HEV take place asymptomatically; it is unknown how many of those exposed have seroconversion to anti-HEV and how many of those infected do not have clinical signs of HEV infection. Chronic infection due to hepatitis E may, in the long term, produce acute liver failure in some patients or chronic liver failure in patients with underlying liver disease. Prior studies have demonstrated that infections due to HEV increase the risk of death up to 70% in cases of a previous liver disease. The typical symptomatology of acute liver failure over chronic hepatitis, lead to acute deterioration of liver function with clinical complications, like ascites, hepatic encephalopathy and/or hepatic coagulopathy[52].

In experimental works, the RNA-HEV has been detected in feces one week before the onset of symptoms and up to two weeks after; in serum of almost all patients, it was possible to detect it two weeks after the start of the disease and continue with positivity from 4 to 16 weeks. In experimental processes, at hepatic level, in experiments, HEV antigens – indicative of viral replication – can be visualized after seven days of infection. The RNA-HEV levels in serum and feces are quite high from the beginning of the infection and fall sharply at the end of it; simultaneously when a high antibody response is given to the vigorous anti-

body response. The pathogenic mechanisms that lead to the extremely high rate of mortality due to fulminant liver failure in pregnant women (20% - 30%) are unknown[17].

The HEV infection in immunosuppressed individuals may take place in chronic manner and lead to potentially deadly cirrhosis. In solid organ transplant receptors, the infection may also occur in chronic manner, especially for liver transplant receptors. A differential diagnosis to consider in these patients with elevated transaminases and which present rejection, must include hepatitis E[51].

The parenteral route in HEV infection, through blood transfusion, constitutes an important form of HEV transmission. The strains related with hepatitis E in these cases are those from genotypes 3 and 4; this post-transfusion risk must be considered[17].

Vaccine

Hepatitis E is increasingly recognized globally as an infection that contributes as global disease burden, but it is underestimated. The subpopulations associated with severe diseases and death include pregnant women, patients with basic liver diseases, and the elderly[52].

Prevention of HEV infection through vaccination is based on the capsid protein, given that it is highly immunogenic and elicits effective neutralizing antibodies[53].

Hecolin® is currently the only vaccine authorized for the prevention of hepatitis E; it was authorized in China and launched in 2012. This vaccine is developed by Xiamen Innovax Biotech Co., Ltd.; however, many obstacles exist for its application[54,55].

The World Health Organization (WHO) has drafted a first document indicating its position on the vaccine against hepatitis E, focused principally on the availability of evidence about the Hecolin® vaccine, the only vaccine against hepatitis E that is currently authorized. The vaccine, which is currently only licensed for use in China in people from 16 to 65 years of age, with high risk of HEV infection, according to occupation or lifestyle, protects against symptomatic infection due to HEV, with an extremely high rate of efficacy against the HEV genotype 4. The WHO considers that data on the protection against genotype 1 are limited and against genotypes 2 and 3 are not available. However, scant information on the vaccine's behavior globally leads the WHO to avoid recommending its introduction for routine use in national vaccination programs, although leaving it to the consideration of local authorities regarding the possibility of deciding to use the vaccine based on the local epidemiology[56].

Conclusions

In summary, Infection by the hepatitis E virus is a serious public health problem in many developing countries, especially in those where there are displaced groups, because the routes of transmission between humans are the contamination of water sources and water sources. poor hygienic conditions. It is also an important health problem for pregnant women due to specific strains and for those immunosuppressed or organ transplant recipients. Little is known about its viral cycle and its cell receptors; Greater understanding is needed on the activity and role of ORF1, ORF2, ORF3, and ORF4 polyproteins relative to genotype 1, which will allow more information for vaccine development. Finally, it is to be recognized that more information is needed on the clinical behavior of the disease, and epidemiological data that help to understand the transmissibility of the virus and the relationship with its hosts.

Ethical disclosures

Protection of human and animal subjects. This research was approved by the Institutional Review Board.

Right to privacy and informed consent. The authors declare that no data that enables identification of patients appears in this article.

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