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Review

Hepatitis E virus and its public health importance: Review

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ABSTRACT

The only member of the genus Herpevirus in the family Herpeviridae is the hepatitis E virus (HEV). It is a single-stranded, spherical RNA virus without an envelope. There is just one serotype of HEV, and there are four known genotypes (1-4). This review's goal is to learn more about the Hepatitis E virus's pathogenesis, epidemiology, transmission, diagnosis, prevention, and control. It is generally regarded as one of the main causes of viral hepatitis worldwide and a serious public health issue in many developing nations, particularly in those where there are displaced populations, because the human-to-human transmission routes involve drinking fecal water contaminated with human waste and living in unhygienic conditions, while in high-income nations it is regarded as a zoonosis spread by eating contaminated food products. Due to certain strains, it is also a serious health concern for expectant mothers, as well as for those with compromised immune systems and organ transplant recipients. Fecal shedding is seen during primary infection with the developing cause of acute hepatitis, the hepatitis E virus (HEV). Pigs raised for domestication are thought to be the main source of HEV-3. Two to nine weeks after HEV exposure, the patient's primary symptoms include myalgia, arthralgia, anorexia, hepatomegaly, fever, weakness, vomiting, and jaundice. Real-time RT-PCR TaqMan assays, which can identify HEV genotypes 1-4 and employ primers from ORF-3, are the most popular method for detecting nucleic acids in human HEV infections. Although there is no specific treatment for HEV infection, patients with chronic hepatitis E include reduction of immunosuppression and administration of pegylated interferon alfa or ribavirin Peginterferon, ribavirin, or a combination of the two agents leads to viral clearance in most patients and a sustained response in a high proportion of patients. Hecolin is currently the only vaccine authorized for the prevention of hepatitis E. It was authorized in China and launched in 2012.

Keywords: Hepatitis E virus (HEV), zoonosis, RT-PCR, pigs, Ribavirin.

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Abbreviations: DcHEV, Dromedary camel Hepatitis E Virus; **EASL,** European Association for the Study of the Liver; **HEV,** Hepatitis E Virus; **HIV,** Human Immune Virus; **NCR,** Non-Coding Region; **ORF,** Open Reading Frame; **RNA,** Ribo Nucleic Acid; **RT-PCR,** Reverse Transcriptase Polymerase Chain Reaction; **UTR,** Untranslated Region; **WHO,** World Health Organization.

INTRODUCTION

One of the main causes of acute viral hepatitis globally is the hepatitis E virus (HEV) (Stanaway et al., 2016). When looking into an outbreak of enterically transmitted non-A, non-B hepatitis in Russian soldiers stationed in Afghanistan in 1981, Russian virologist Mikhail S. Balayan made the discovery. Balayan self-administered a stool extract from the sick soldiers and afterward experienced hepatitis symptoms. His stool samples examined by electron microscopy revealed spherical non-enveloped virus particles (Lemon and Walker, 2019). The only hepatitis virus with an animal reservoir is this one (Khuroo, 2011). HEV is a rapidly spreading infectious agent that primarily causes acute infections and is a significant contributor to the water-borne hepatitis epidemic in tropical and subtropical nations with unsanitary environments. In many nations, the illness is

widespread on continents including southeast and central Asia, the Middle East, and Africa (Aggarwal and Jameel, 2011).

The main cause of acute viral hepatitis in humans is the tiny RNA virus known as hepatitis E virus (HEV). The majority of HEV cases in Europe are caused by genotype 3, which is spread by improperly cooked meat, close contact with infected animals, and tainted blood products. In Europe, there are at least 2 million locally acquired HEV infections each year. Usually self-limiting and subclinical acute HEV infection (EASL, 2018). Both industrialized and developing nations are currently dealing with the hepatitis E virus (HEV) as a public health issue (Ju and Ding, 2019). There are 8 genotypes of the HEV genome (HEV-1 to HEV-8), however only genotypes 1-4 can infect people. Genotypes 1 and 2 have primarily been found in Asia and Africa and are associated with the fecal-oral transmission, while genotypes 3 and 4 are known as zoonosis and spread among both animals and people. Global documentation of genotype 3 is available (Bruni et al., 2018). 20 million persons were infected with HEV in 2005, according to a modeling study supported by the World Health Organization (WHO), with an estimated 3.3 million clinical cases, 70,000 deaths, and 3000 stillbirths, predominantly in Asia and Africa (Rein et al., 2012).

The World Health Organization (WHO) launched a global strategy to stop viral hepatitis transmission in 2016, recommending that persons with viral hepatitis have access to safe, accessible, and effective prevention, care, and treatment services by 2030, the goals are to reduce the number of new instances of hepatitis by 90%, treat 80% of eligible patients infected with viral hepatitis, and reduce the number of hepatitis-related fatalities by 65 percent. This virus causes 3.3% of all deaths due to hepatitis worldwide. HEV accounted for 1.7% of the total global healthy years of life lost (738,508 disability-adjusted life years) due to hepatitis in 2017 (WHO, 2016, 2019).

The most affected populations are among the world's most vulnerable groups – pregnant women and their neonates, as well as displaced persons and those living in resource-limited settings with poor access to clean water and sanitation. HEV is a significant contributor to global maternal mortality, with reported case-fatality rates of 20 to 30% in pregnant women with the symptomatic disease (Azman et al., 2019). It is responsible for a liver disease that affects millions of people worldwide, especially in low and middle-income countries (Blasco-Perrin et al., 2016).

Generally, the HEV disease is self-limiting and has mild symptoms; however, in some cases, it can result in severe acute hepatitis, extra-hepatic disorders, chronic hepatitis leading to cirrhosis, and fulminant hepatitis (Kamar et al., 2014). Pregnant women have been documented to have an increased risk of fulminant hepatitis (Kumar et al., 2004).

In addition to environmental risks, host factors may also play a role in HEV susceptibility. Blood antigens are known to act as receptors for host immune and inflammatory responses and can mediate innate responses to invading pathogens. The ABO erythrocyte antigen system and Rh (D) phenotype play important roles in clinical practice. Associations between the ABO blood group and susceptibility to infection and infection-associated disease severity have been described for other liver pathogens such as the hepatitis B virus (Jing et al., 2020). The highest seroprevalence (50.01%) was reported in North Africa followed by East Africa (35%) (Dagnew et al., 2019). Moreover, there is a report of the seroprevalence of HEV in pigs in developing countries such as Cameron at 43.2% (Modiyinji et al., 2018). In Ethiopia, there is a report of high seroprevalence (31.6%) of HEV in pregnant women (Abebe et al., 2017). In animals there is a report which revealed that 22.4% of Ethiopian dromedary camels were positive for anti-DcHEV IgG (Li et al., 2017), suggesting that the dromedary camel HEV (DcHEV) infection is circulating in the dromedary camels in Ethiopia. In addition to camels, studies indicated that swine and human HEV strains are genetically very close and cross-species transmission has been proved (Meng et al., 1998). Therefore the objective of this review is to access the pathogenesis, epidemiology, transmission, diagnosis, privation and control of the hepatitis E virus.

LITERATURE REVIEW

Etiology

The family Hepeviridae is divided into two genera, Orthohepevirus, which contains HEVs that affect mammalian and avian species, and Pescihepevirus, which contains HEVs affecting cutthroat trout. The Orthohepevirus genus is further divided into four different subgenera depending upon the species affected. Orthohepevirus A contains HEVs of humans, pigs, wild boars, deer, mongoose, rabbit, and camel. Orthohepevirus B contains chicken HEV. Orthohepevirus C contains HEVs of rats, shrews, ferrets, and mink. Orthohepevirus D contains HEV isolated from bats (Perez-Gracia et al., 2015). Hepatitis E virus (HEV) is a small, spherical, non-enveloped, positive-sense single-stranded RNA virus with icosahedral capsid symmetry. It belongs to the genus Orthohepevirus in the family Hepeviridae (Thiry et al., 2017).

Pathogenesis

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

known (Kang and Myoung, 2017). 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 a cytopathic effect, liver damage may be due to cytotoxic T lymphocytes and natural killer cells (Horvatits et al., 2019).

Hepatitis E is caused by the hepatitis E virus (HEV), one of the five main hepatitis viruses (WHO, 2021). Eight HEV genotypes have been described, of which four main HEV genotypes are known to infect humans (Smith et al., 2020).

Hepatitis E is increasingly recognized globally as an infection that contributes to the global disease burden, but it is underestimated. The subpopulations associated with severe diseases and deaths include pregnant women, patients with basic liver diseases, and the elderly (Zhang et al., 2016). HEV infection in pregnancy caused by genotypes 1 and 2 in developing countries has been associated with poor fetal-maternal outcomes as compared to the relatively benign course of illness in the Western world where infections are more commonly caused by genotypes 3 and 4 (Kar and Sengupta, 2019). Data from the previous study shows HEV infection to have a higher incidence, a severe and aggressive course of illness, and poor outcomes during pregnancy (Karna et al., 2020). In pregnant women, HEV was the leading cause of acute viral hepatitis and acute liver failure accounting for 80.36% (442/550) and 73.38% (102/139) of cases, respectively. HEV-related liver infection accounted for 98/129 (75.96%) death cases, whereas non-HEV liver infection accounted for 31/129 (24.04%) death cases in comparison among pregnant women. The course of illness is worse if the infection is acquired in the third trimester of pregnancy. An interesting study from Egypt showed high anti-HEV prevalence (84.3%) among pregnant women, but many of them never recalled an episode of viral hepatitis (Kar and Sengupta, 2019). The differences in severity and prognosis in the different parts of the world could be accounted for by infections caused by different genotypes, differences in the rates of childhood infections, healthcare facilities and maternal nutritional state. Fetal complications of HEV infection range from preterm delivery, intrauterine death, and poor infant survival rates (Krain et al., 2014). In a study by Rayis et al. (2013), out of 39 pregnant women with HEV infection, there were 14 intrauterine deaths and 9 premature deliveries. Currently, there is no evidence of any therapeutic benefit of termination of pregnancy in HEV-induced. EASL recommends treatment of HEV genotypes 1 and 2 infections during pregnancy in high-dependency units and prompt transfer to Liver Transplant Unit if liver failure develops (EASL, 2018).

Epidemiology

Hepatitis E is hyperendemic in many countries located in southeast Asia (Burma, Cambodia, Indonesia, Thailand, Vietnam and Laos), southern Asia (India, Bangladesh, Bhutan, Nepal, Pakistan and Sri Lanka), central Asia (Kazakhstan, Tajikistan and Uzbekistan); east Africa (Kenya, Uganda and Burundi), north Africa (Algeria, Morocco, Sudan and Tunisia), west Africa (Ivory Coast, Liberia, Nigeria and Mali) and some countries in North America (Mexico) (Khuroo, 2011). It is endemic in many countries of the Middle East (Turkey, Saudi Arabia, Yemen, Libya, Oman, Bahrain, Iran, Kuwait and the United Arab Emeritus), some regions of Southeast Asia (Singapore) and South America (Brazil, Argentina, Ecuador and Uruguay). Hepatitis E is responsible for more than one-fourth of all cases of acute sporadic hepatitis and fulminant hepatitis (Ghabrah et al., 1995) (Figure 1).

There are 2 epidemiological patterns for HEV infections: epidemic and non-epidemic (Rodriguez et al., 2012). The epidemic pattern has been observed mainly in India, China, North and West Africa. In these cases, contaminated bodies of water are the main sources of infection. Usually, the population affected consists of young adults between 15 and 30 years of age (Purcell and Emerson, 2008; Rodriguez et al., 2012). In Latin America, the only outbreaks that have been reported occurred in Mexico in 1986 and 1987 (Aggarwal and Naik, 2009). The non-epidemic pattern occurs in industrialized countries where sporadic cases can be related to the zoonotic character of genotypes three and four (EASL, 2018).

Accurate estimates of HEV disease burden in both endemic and non-endemic regions have been challenging to obtain. In many endemic areas, lack of clinical awareness and lab testing capabilities present significant barriers to diagnosis, and often the only documented cases are those severe enough to require hospitalization. Few low-income countries have hepatitis E surveillance, though some sentinel sites have been established in highly endemic areas such as Bangladesh and Nepal, with support from international funding and resources (Izopet et al., 2015). Recent outbreaks have occurred in Chad and the Ganges River Basin in northern India (Ray, 2019). Of the estimated 20 million yearly HEV infections worldwide, 60% are thought to occur in East and South Asia (Rein et al, 2012).

The first large retrospectively identified hepatitis E outbreak occurred in India in the mid-1950s (Teshale and

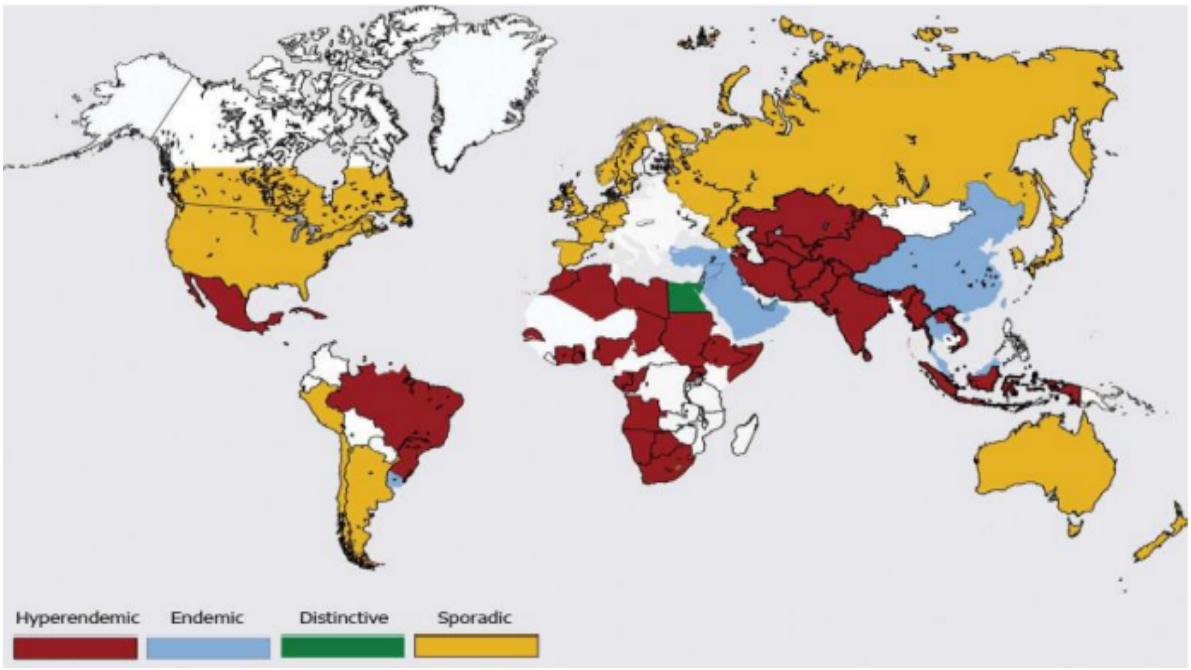

Figure 1. Geographic distribution of the hepatitis E virus (Khuroo, 2016).

Hu, 2011), and outbreaks continue to be reported there today, with 27% of the recorded water-borne hepatitis E outbreaks between 1980 and 2017 reported in northern India (Carratala and Joost, 2019). Other countries in Asia that have reported outbreaks include Bangladesh, Pakistan, Nepal, and Indonesia (Hakim et al., 2017). According to a recent geographic modeling analysis, outbreaks in Asia tend to have higher average case numbers (7677 cases/outbreak) than those in Africa (1436 cases/outbreak) (Carratala and Joost, 2019). The first well-documented HEV outbreak in Africa occurred in Somalia in 1988–89, with more than 11,000 cases. Large outbreaks have occurred in refugee camps in Sudan, South Sudan, Chad, Darfur, and Kenya (Hakim et al., 2017). A recent meta-analysis of 22 pooled studies found an HEV seroprevalence of 29% among pregnant women in Africa (Dagnew et al., 2019). Another meta-analysis of 29 studies measuring HEV prevalence in acute hepatitis patients in Somalia found an overall prevalence rate of 47% (Hassan-Kadle et al., 2018), and a recent survey of 1000 adults in Uganda found a similar seroprevalence rate of 47% (Boon et al., 2018). The epidemiology of hepatitis E in Egypt is somewhat paradoxical, in that the seroprevalence of HEV1 is very high with a low incidence of symptomatic infection (Hasan et al., 2016). In industrialized countries, zoonotic HEV3 and HEV4 infections predominate, usually due to consuming undercooked meat, especially pork (Webb and Dalton, 2019). A recent meta-analysis of 26 studies from 15 industrialized countries (including Europe, Australia, New Zealand, and North America) found a wide range of HEV seroprevalence rates, ranging from less than 5% to greater than 50% (Capai et al., 2019). There is increasing evidence that factors such as viral subtype, infectious dose, food, and host factors such as genetics or nutrition status contribute to the variation in hepatitis E epidemiologic patterns in different regions of the world (Krain et al., 2014; Kamar et al., 2017). There are seven genotypes of HEV, viz. HEV 1–7, but only a single serotype. HEV 1–4 are known to infect humans, while HEV 5–7 have animals as their host only. There are two different epidemiological patterns of HEV. HEV genotypes 1 and 2 cause outbreaks, mostly in hyperendemic regions of the world. Mostly young adults are affected, and the disease is particularly troublesome for pregnant women who develop a very severe form of the disease (Kamar et al., 2017). In animals, there is a report that revealed that it affects domestic animals like pigs and camels (Haimanot, 2020).

Transmission

The major way of HEV transmission is primarily by the fecal-oral route and has been reported to occur as large waterborne epidemics and small outbreaks in developing countries. So its infection was first described as a waterborne disease, transmitted through drinking fecally contaminated water (WHO, 2019). Similarly, a lack of hygienic measures, such as a lack of hand washing or the absence of proper sanitation, is an important risk factor for the acquisition of HEV in the general population (WHO, 2014). Undercooked or raw pork meat, liver, and infected cow's milk are some known sources of HEV

infection in these regions (Goel and Aggarwal, 2016). In different geographical areas, frequent and continuous detection of specific HEV types in the same species clearly indicates a true animal reservoir as represented by domestic pigs, wild boars, chickens, and rats. In other animal species where HEV is detected sparsely, this suggests spill-out infections rather than a true reservoir host (Kenney, 2019). Therefore Hepatitis E is considered a zoonotic infection with pigs and wild boars serving as the main reservoir for human infections (Mirazo et al., 2014). Domestic pigs are considered the main reservoir of HEV-3 (Ricci et al., 2017). Food-borne transmission of HEV-3 via consumption of raw pig liver sausage (figatelli) has been supported by epidemiological and virological findings (Colson et al., 2010) and the presence of infectious HEV was demonstrated in pork sausages and pork livers (Berto et al., 2013). Transmission may occur vertically. Preterm delivery in mothers with hepatitis E is common and associated with poorer neonatal survival (Sookoian, 2006). Other less common routes are blood transfusion and organ transplanting HEV infection elicits both immunoglobulin M (IgM) and IgG antibodies against HEV. The IgM anti-HEV response is rapid, occurring about a month after infection and peaking at the time of onset of biochemical abnormalities and/or symptoms (Tsarev et al., 1992).

Virus replication

At the 5′ end of the genome, there is a tiny non-coding region (NCR; 1–25 bp) followed by open reading frame 1 (ORF1), which codes for the non-structural proteins needed for replication (5109 bp; expected molecular mass: 185 kDa). A little cis-reactive element divides ORF1 from the two bicistronic overlapping reading frames, ORF2 and ORF3 (CRE site). The 3′ end also contains an untranslated region (UTR) and a poly (A) tail. After the polyprotein is translated (Figure 2B), the replication of the viral RNA by RdRp proceeds with the synthesis of the negative strand RNA (Figure 2C). Based on the negative strand, two different RNAs are synthesized, the full-length genomic RNA (D) and a 2.2 kb subgenomic RNA (D) (Sookoian, 2006). The genomic RNA serves as a template for ORF1 translation and is packaged into viral particles or serves as a template for the synthesis of additional negative-strand RNA, whereas the subgenomic RNA serves as a template for the translation of the capsid protein (72 kDa) and the ORF3 protein (E) (13 kDa) (Tsarev et al., 1992) (Figure 2).

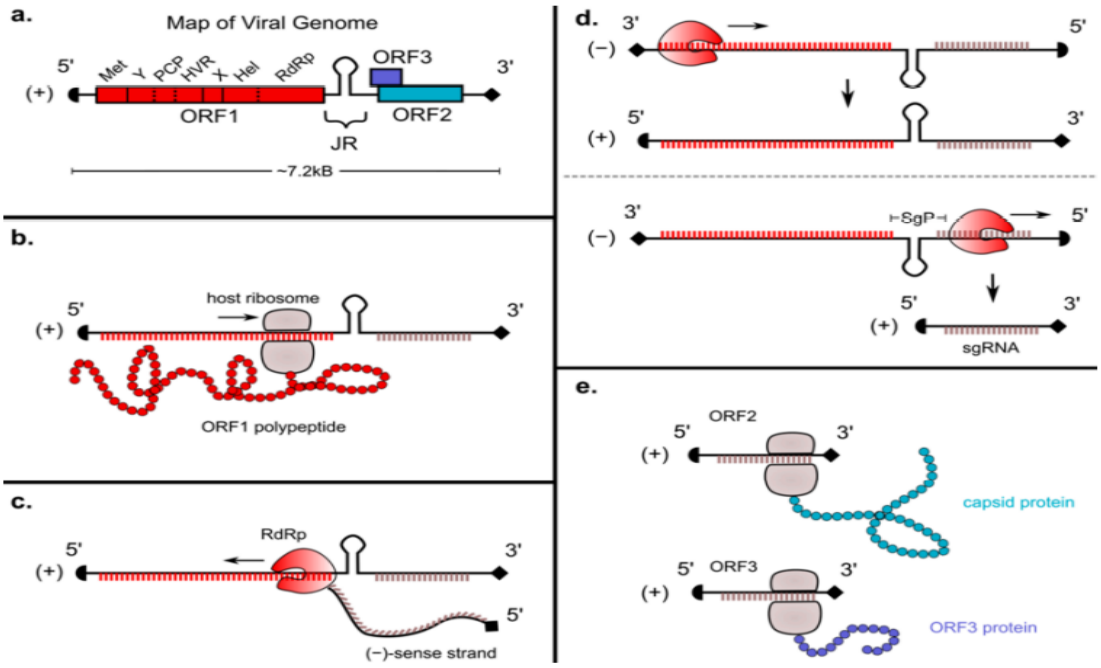

Figure 2. Genomic organization and replicative mechanism of hepatitis E virus (Graff et al., 2006).

Hepatocytes are polarized epithelial cells in vivo, which have an interestingly organized extreme with particular apical (confronting the bile canaliculi) and basolateral (facing the hepatic sinusoid) spaces in physiological conditions (Himmelsbach et al., 2018). The progeny virions can release at both the apical and basolateral

membranes of infected hepatocytes. Studies have found that ORF3 is mainly located close to the bile canaliculi of hepatocytes *in vitro* (Robert et al., 2019) and in vivo (Emerson et al., 2010). Most infectious HEV particles as enveloped (eHEV) form are released from the hepatocyte via its apical domain into the bile canaliculi, where they enter the biliary tract and are subsequently shed into faeces, while a small fraction of HEV particles (as eHEV form) are released from the basolateral domain into the blood, where they can spread throughout the host. Enveloped (eHEV) released from the apical domain enters the bile, and the eHEV membrane is degraded by the detergent action of bile, resulting in non-enveloped HEV in faeces (Capelli et al., 2019) (Figure 3).

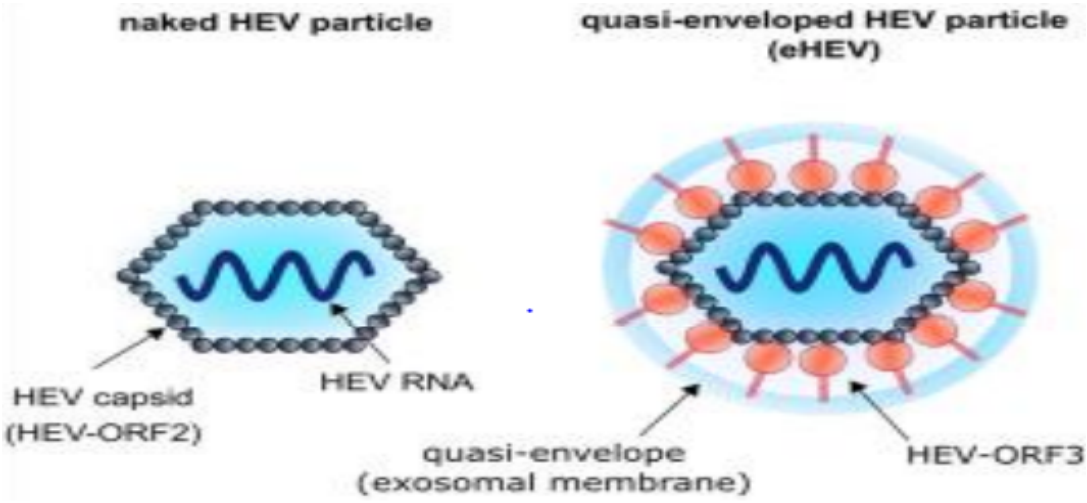

Figure 3. Representation of enveloped and naked hepatitis E virus (Tsarev et al., 1992).

Clinical sign

In the majority of patients, HEV causes a self-limiting and usually asymptomatic infection (Purcell and Emerson, 2008). Clinical signs and symptoms such as myalgia, arthralgia, anorexia, hepatomegaly, fever, weakness, vomiting, and jaundice emerge two to nine weeks after HEV exposure. In rare and severe cases, HEV can cause abrupt liver failure. Chronic instances are uncommon; however, they can occur in immune-compromised persons (Mirazo et al., 2014). The HEV infection is usually asymptomatic, and jaundice occurs in 5 to 30% of infected patients (Tsarev et al., 1992). 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% (Yin et al., 2016).

Despite starting as an asymptomatic event most of the time, 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 (Lhomme et al., 2020). The range is 15 to 64 days; the mean incubation period is around 6 weeks but has varied from 26 to 42 days in different epidemics (Thakur et al., 2020). Chronic infections have been associated with genotype three in patients receiving immunosuppressive therapy for organ transplantation, patients infected with HIV, and patients undergoing chemotherapy (Table 1) (Kamar et al., 2011; Heymann, 2015).

It should be borne in mind that the epidemiological weight is still unknown, but it is suggested that patients receiving immunosuppressive therapy for organ transplantation and HEV infections may rapidly progress to hepatic fibrosis and then to cirrhosis (Gerolami et al., 2009).

Diagnosis

Acute HEV infection is usually diagnosed by detecting specific anti-HEV antibodies (IgM and IgG). However, the performance of the available assays in different settings is not optimal, and highly variable values are observed depending on the commercial assay employed (Kamar et al., 2016). HEV nucleic acids traditionally have been detected using a semi-nested reverse transcriptase polymerase chain reaction (RT-PCR) assay (Rossi-Tamisier et al., 2013). Primers amplify a segment of the HEV ORF2, which encodes the immunogenic capsid

Table 1. Acute and chronic HEV infections.

Causative genotype	Patient characteristics	Characteristics of infection	Extrahepatic manifestations	References
Acute infections (1,2,3,4)	Patients between 15 and 30 years have infections caused by genotypes 1 and 2. Patients older than 30 years usually have infections caused by genotypes 3 and 4.	Symptoms include fever, nausea, abdominal pain, vomiting and jaundice. Anti-HEV IgM between the second and fourth week after infection.	Neurological disorders: Guillain Barre syndrome Bell's palsy Neuralgic amyotrophy Acute transverse myelitis Encephalitis Hematological disorders Thrombocytopenia Aplasticanemia Pancreatitis Kidney injuries: Glomerulonephritis	Tsarev et al., 1992; Mirazo et al., 2014 and Yin et al., 2016
Chronic infections (3)	Patients with immune system deficits due to: Immunosuppression following Transplant HIV infection Chemotherapy Leukemia	Fatigue is the primary symptom. High levels of liver enzymes. Infection can progress to cirrhosis. High concentration of anti-HEV IgG antibodies	Neurological disorders: Guillain Barre syndrome Bell's palsy Neuralgic amyotrophy Acute transverse myelitis Encephalitis Kidney damage: Glomerulonephritis	Kamar et al., 2011 and Heymann, 2015

protein (Thiry et al., 2017). A comparison has been done of two single-plex real-time RT-PCR assays and two duplex real-time RT-PCR assays for the detection and differentiation of HEV genotypes in swine (Williams et al., 2001). The most widely used assay for the detection of nucleic acids in human HEV infections is a real-time RT-PCR TaqMan assay which uses primers from ORF-3 and can detect genotypes HEV-1–4. This assay can detect 0.12 PID_{50} swine HEV even in environmental samples, which is greater than the nested RT-PCR (Gerber et al., 2014).

HEV isolation is difficult; the virus is uncultivable in cell culture (Jothi et al., 2006). However, recombinant capsid proteins can be expressed using Escherichia coli, containing a cloned capsid gene, and purified to hyper immunize animals for diagnostics (Meng et al., 2006). Immunohistochemistry has been used to detect HEV-3 antigens in tissues and characterize the type and severity of the inflammatory process by binding to CD3 surface receptors on porcine immune cells. Viral antigens have been detected using rabbit anti-HEV-3 hyperimmune serum using recombinant capsid proteins (Lee et al., 2013). In situ hybridization has also been used to detect HEV RNA in tissues (Schlosser et al., 2014).

Treatment

HEV infection is usually self-limiting and so only supportive treatment is needed. There is no established therapy for hepatitis E virus (HEV) infection. The successes with ribavirin have led to its use for severe, acute hepatitis E, with promising results (de Deus et al., 2007), but ribavirin is contraindicated in pregnancy due to teratogenicity and fetal loss (Hoofnagle et al., 2012). Liver transplantation is the only treatment for patients with fulminant hepatic failure (Levick, 2014). Treatment options for patients with chronic hepatitis E include reduction of immunosuppression and administration of pegylated interferon alpha or ribavirin Peginterferon, ribavirin, or a combination of the two agents leads to viral clearance in most patients and a sustained response in a high proportion of patients. Ribavirin alone in doses of 600 to 800 mg daily for 12 weeks yields sustained virologic responses in at least two-thirds of patients with chronic hepatitis E (Kamar et al., 2014). HEV reinfection has been described. Furthermore, in immune-competent patients, an IgG antibody concentration of 2.5 WHO units/ml could protect against reinfection (Wedemeyer et al., 2012), in immune-compromised patients, this titre can be increased up to 7 WHO units/ml (Zhang et al., 2015).

Prevention and control

The most effective preventative measure for HEV infection is to avoid contact with the source of infection, such as avoiding the consumption of raw/undercooked food where HEV has been isolated or the consumption of unchlorinated contaminated water in low-income countries (Rivero-Juarez et al., 2020). Treating meat at a temperature of 70°C for 30 min has been shown to strongly inhibit HEV activity (Johne et al., 2016). For contaminated milk, thermal treatment at 100°C has shown complete inactivation of the virus (Huang et al., 2016). For contaminated water, a chlorine dose of 5 mg/L for 15 min appears to be sufficient to reduce the HEV viral load; nevertheless, it may be necessary to increase the chlorine dose if the water contains solid material (Ricci et al., 2017).

Currently, there is only one vaccine available for the prevention of HEV infection, which is a recombinant

vaccine against genotype 1 that has demonstrated high protection of up to 5 years for people over 16 years of age, with potential protection of up to 30 years (Wedemeyer et al., 2012). 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 to its application (Zhang et al., 2016). This position is supported by the fact that no clinical trials are evaluating the safety and efficacy of this vaccine in populations susceptible to a worsened prognosis of the disease (HIV-infected patients, transplant recipients, pregnant women, and patients with underlying chronic liver disease) and because of only demonstrated efficacy in preventing HEV genotype 1 infection. For this reason, the WHO recommends that vaccination should be considered individually in people who plan to travel to an area where an epidemic is occurring like aid workers and health workers (Rivero-Juarez et al., 2019). Prevention of HEV infection through vaccination is based on the capsid protein, given that it is highly immunogenic and elicits effective neutralizing antibodies (Mazalovska and Kouokam, 2020).

CONCLUSION AND RECOMMENDATIONS

In general, HEV is the leading cause of non-A, non-B enterically-transmitted acute viral hepatitis in endemic regions and is considered a major global health problem that causes significant morbidity worldwide. Zoonotic transmission seems to be a major cause of HEV infections in industrialized countries, in the form of sporadic autochthonous cases. As the observation of pigs grazing in the field and around watering points, suggests possible environmental contamination of the virus that could lead to the infection of susceptible animal species including humans. The virus is the leading cause of enterically-transmitted viral hepatitis in humans globally. These viruses are transmitted by the faecal-oral route and many of the environmental and socio-economic factors foster the transmission routes. It also leads to outbreaks in developing countries and causes significant morbidity and mortality in immune-compromised and pregnant females. Further research into therapeutic options for treating hepatitis E infection is the need of the hour. Oral ribavirin is the initial drug of choice for severe acute hepatitis, acute-on-chronic liver failure, and chronic hepatitis E. But if repeatedly used, it may form drug resistance. So our further focus should be on finding appropriate management options for HEV infection during pregnancy and for ribavirin-resistant infections. Also, we keep the prediction method for decreasing the spread of the virus.

Based on the above conclusions the following recommendations are forwarded:

- Most different sources are available on serological tests, and only a little molecular diagnosis is there, therefore I want to recommend that more molecular tests publication should be seen in the future.
- Scientists should focus on producing effective vaccines and medicines that are used for the prevention and control of the disease because the disease is highly pathogenic.
- Governments of different countries should be aware of their citizens about the disease in detail and work on prevention.

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