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Review Article

HEPATITIS E VIRUS: A REVIEW

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Hepatitis E virus is the last of the five hepatotropic viruses to be discovered. Originally, it was considered that the disease is an acute, travel-associated self-limiting illness limited to humans, but new studies prove that there are animal reservoirs and zoonotic transmission is possible. In addition, HEV is currently considered as a major public health burden all over the world, resulting in significant morbidity and mortality. Therefore, the issue of hepatitis E infection is of re-emerging importance because the questions such as the transmission of HEV especially in developed countries, treatment and vaccination options are yet to be discovered. This review presents a literature review of hepatitis E and highlights the importance of identifying new diagnostic methods and drugs for HEV.

Keywords: Hepatitis E, Genotypes, Epidemiology, Prevention

INTRODUCTION

Hepatitis E is the fifth recognized human viral hepatitis and is probably the most common cause of acute viral hepatitis in the world (Hoofnagle *et al.,* 2012; and Krawczynski *et al.,* 2013). However, in developed countries, Hepatitis E Virus (HEV) is responsible for less number of cases, hepatitis A virus being the most prevalent (Dalton *et al.,* 2008; and Purcell and Emerson, 2008). Although hepatitis E virus is an important cause of hepatitis and is broadly studied, there is little understanding about its mechanism of replication and pathogenesis. HEV infection was not discovered until 1980. It was first identified in 1980 through investigation of blood samples from patients affected by an acute hepatitis endemic in New Delhi (India) from 1955 and 1956, spread by contaminated water. "The enteric non-A hepatitis virus", the causal agent in this epidemic was visualized in 1983 under electron microscope by Russian virologist Mikhail Balayan while investigating his own stools after self-administration of contaminated material and was named 'E' after its endemic and enteric characteristics (Hoofnagle *et al*., 2012).

The occurrence of acute hepatitis E infection is supposed to cause 3 million human cases per year all over the world, with approximately 70,000 deaths (Murali *et al.,* 2015). Maximum number of cases are observed in endemic countries, however the incidence of hepatitis E infection in low-endemic areas has risen (Murali *et al.,* 2015).

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Seroprevalence of HEV in developing countries is high, for example India and Southeast Asia, ranging from 27-80% (Hoofnagle *et al.,* 2012; and Murali *et al.,* 2015). Interestingly, studies in developed nations such as the United Kingdom and the United States of America have proved surprisingly high seroprevalence (21-25%) of HEV. The studies attributed high prevalence of HEV to factors such as subclinical infection, exposure to animal, cross-reactivity with other agents or false positive test results (Murali *et al.,* 2015). Mortality in the acute form of infection is 1-4% and pregnant women and immunodeficient patients have higher risk of fatal infection (Murali *et al.,* 2015).

VIROLOGY

Hepatitis E virus is a small non-enveloped virus with 27-34 nm diameter and a single-stranded RNA genome (Ahmad *et al*., 2011). It replicates in the cytoplasm of cells and it can also replicate in hepatocytes, small intestine, colon cells and lymph nodes (Kumar *et al.,* 2013). HEV belongs to genus *Hepevirus*, in the family *Hepeviridae* (Krzowska-Firych *et al.,* 2018).

HEV is differentiated based on the nucleotide sequences of the genome and is categorized as a single serotype with four major genotypes [HEV 1-4], with each genotype having several subtypes. Genotype 1 is divided into five subtypes (1a-1e) and has been isolated from tropical as well as some subtropical countries in Asia and Africa. Genotype 2 which has two subtypes (2a and 2b), has been isolated from Mexico, Nigeria and Chad (Pelosi and Clarke, 2008). Genotype 3 that has ten subtypes (3a-3j) often affects the elderly and has been found all over the world, i.e., from Asia, Europe, Oceania, North and South America. Genotype 4 has seven subtypes (4a-4g) but has been isolated from limited areas, mainly from Taiwan and China. The most commonly recognized causative agent of hepatitis E in developing countries are genotypes 1 and 2, which are limited to humans and are particularly linked with males, with larger epidemics and outbreaks in developing countries with poor sanitation, whereas genotypes 3 and 4 infect humans, pigs and other animals, and have been observed to produce sporadic outbreaks in both developed and developing countries (Krzowska-Firych *et al*., 2018).

EPIDEMIOLOGY

Based on seroprevalence, it is projected that one-third of the world's population has been infected with HEV (Hoofnagle *et al.,* 2012). The average incubation period of HEV is 40 days, and the highest rate of infection is between 15 and 40 years of age (Shrestha *et al.,* 2007). The incidence of disease is more in men than women, with a ratio of 2:1 in developing countries and >3:1 in developed countries (Kumar *et al.,* 2013). Each year, HEV is believed to cause roughly 20 million infections, subsequently resulting in three million acute illness and 57,000 deaths (Lozano *et al.,* 2010). The first well-documented outbreak of HEV occurred in New Delhi, India during the year 1955-1956 that affected nearly 30,000 people and it was caused due to contamination of drinking water supply with fecal matter. Originally, it was though that the outbreak was caused by HAV, however, a backdated analysis of stored sera of affiliated patient proved that it was because of a new infectious agent – HEV (Krzowska-Firych *et al*., 2018).

Hepatitis E virus is excreted in the feces of infected person and is spread by different routes such as fecal-oral, water contamination, ingested

food, infected animals (raw or undercooked pork, wild boar, deer meat or entrails), zoonoses, exposure of humans to body fluids of infected animals (Kumar *et al.,* 2013, WHO). Other modes of transmission include transfusion of contaminated blood products, vertical transmission and transplantations with HEV-infected grafts (Matsubayashi *et al*., 2008). However, contaminated water is the most common mode of infection (Meng *et al.,* 2011); it is always not possible to establish the link between infection and its source, especially in low endemic regions and in sporadic cases in hyperendemic regions. Swine, wild boars, deer and camels have been documented as the zoonotic reservoirs of the infection (Woo *et al.,* 2014; and Lee *et al.,* 2016).

Hepatitis E presents two distinct epidemiological patterns in different epidemiological regions. In the first pattern, large outbreaks affecting hundreds to thousands of people are seen in hyperendemic regions and usually the source of infection is contaminated water (WHO). These regions comprise of developing countries where sporadic as well as epidemic outbreaks of hepatitis E occurs. Genotype 1 is the predominant cause of the disease with higher mortality in pregnant women (Hoofnagle *et al*., 2012). In the second one, which is commonly observed in low endemic regions, zoonotic transmission has an significant role. Developed countries such as the Americas and Europe are included in these regions, wherein HEV infection occurs as scattered cases and small outbreaks. Such outbreaks are the results of exposure to pigs and consumption of undercooked pork. These cases are often caused due to apparently less virulent genotypes 3 and 4 with higher mortality in older adults (Purcell and Emerson, 2008; and Hoofnagle *et al*., 2012).

CLINICAL PRESENTATION

The common symptoms of hepatitis such as fever, nausea, abdominal pain, vomiting, anorexia, malaise and hepatomegaly appear after an incubation period of 2 to 6 weeks (Kamar *et al.,* 2014; and Ahmed *et al.,* 2015). About 40% of symptomatic cases in developing countries and up to 75% of symptomatic cases in developed countries show signs of jaundice (Kamar *et al.,* 2014). The symptoms of infection and jaundice last from days to weeks (Hoofnagle *et al*., 2012). Moreover, hepatitis E can result in acute liver failure (Guerra *et al.,* 2017). Other neurological manifestations include Guillain-Barrésyndrome, Bell'spalsy, acute transverse myelitis and acute meningo-encephalitis (Fujiwara *et al.,* 2014).

The majority of cases in hyperendemic regions show acute and self-limited jaundice, with spontaneous resolution and viral clearance within 1 to 3 months (Guerra). Furthermore, in these areas, asymptomatic infection is also common with milder liver injury and with non-specific symptoms similar to acute febrile viral illness without jaundice. Involvement of liver in such patients is identified only after laboratory examination (Aggarwal, 2011). On the other hand, in low-endemic regions majority of cases are documented during examination of unexplained hepatitis and are sporadic (WHO). Disease in these areas shows some different characteristics from those of high endemic regions. These comprise older age, a well demarcated male predominance, absence of severe infection in pregnant women, a higher incidence of underlying liver disease or alcohol use, relatively higher occurrence of non-specific

symptoms and a higher mortality ratio (Aggarwal, 2011). Genotype 3 infections can be subclinical in young and healthy population, while are usually symptomatic and result in jaundice in older men or patients with considerable comorbidities with poor prognosis (Davern *et al.,* 2011).

DIAGNOSIS

Hepatitis E is an underdiagnosed disease, partially because of the use of serological tests having low sensitivity. Indirect diagnosis can be done by identifying antibodies in the serum against HEV or by directly detecting the genome of the virus in blood or other body fluids. Genotype-specific serological test is not available for diagnosis of HEV (Kamar *et al.,* 2014). RNA of hepatitis E in the blood becomes untraceable around 3 weeks after the initiation of symptoms however can be detected in the feces for more 2 weeks. There is no connection between levels of viremia and intensity of symptoms (Kamar *et al.,* 2014). Therefore, the initial analysis for diagnosis of hepatitis E should be aimed at identifying the anti-hepatitis E IgM antibody. Chronic hepatitis E is diagnosed by the detection of RNA of HEV in stools or serum after at least 3 to 6 months after the diagnosis of hepatitis E. Thus, serological tests identifying anti-HEV IgG and IgM antibodies are not used diagnose chronic disease (Murali *et al.,* 2015).

TREATMENT

In majority of cases of immune competent patients with HEV infection, treatment is not needed because normally it gets cleared spontaneously and symptomatic treatment is needed only occasionally. However, ribavirin can be given to an immune competent patient with severe acute HEV infection (Geolami *et al.,* 2011). Ribavirin therapy is contraindicated in women with pregnancy because of the teratogenicity of the drug, but the risk of untreated HEV to both the foetus and mother is high; therefore, antiviral therapy must be given a thought (Krzowska-Firych *et al.,* 2018).

PREVENTION

Prevention strategies in endemic areas should include improving hygiene and sanitary practices, while in non-endemic areas, it is important to avoid consumption of raw or uncooked meat (Kumar *et al.,* 2013; and Murali *et al.,* 2015). Having good sanitation practices and accessibility of uncontaminated drinking water by the establishment of an appropriate disposal systems for human faeces helps prevent HEV infection; boiling and chlorination of water inactivates HEV. Furthermore, maintaining good hand hygiene practices after using the lavatory and avoiding ice cubes is an additional preventative measure. HEV is thermally stable after heating to 56 °C for one hour; nevertheless, HEV can be inactivated by heating at 71 °C for twenty minutes (Barnaud *et al.,* 2012). Therefore, avoiding the consumption of uncooked meats, as well as the ingestion of raw pork and venison is a measure to reduce the possibility of an infection from HEV3.

Till now, two vaccines have been developed for HEV. The first recombinant viral protein vaccine was established in the 1990s and tested in a high risk population in Nepal. It was found to be safe as well as had an efficacy of 95.5%, but due to the rarity of hepatitis E infection at the time in developing countries, research was not sustained because of the lack of profitability. A recombinant HEV vaccine was developed in 2007 and tested on 2,000 healthy Nepalese males. After three doses, 95.5% of the patients developed anti-HEV

antibodies (Shrestha *et al.,* 2007). In recent times, The People's Republic of China has developed a vaccine, HEV 239, which is expressed in *Escherichia coli* and occurs as a virus-like particle of 23 nm in diameter. This vaccine is presently approved only in the People's Republic of China (Zhu *et al.,* 2010).

CONCLUSION

Globally, hepatitis E is an important cause of acute viral hepatitis and in some countries it accounts for the maximum cases of hepatitis. In spite of this, it still poses numerous challenges and is not completely understood. It remains underdiagnosed, probably due to lack of standard diagnostic methods. Additionally, it is a potentially preventable disease by simple hygienic measures and caution in food consumption. Furthermore, it can be treated with the medication which is available around the world and has resulted in improvement in the prognosis of immunosuppressed patients. Nonetheless, further studies in understanding pathogenesis and development of accurate diagnostic methods and new drugs are essential.

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