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ORIGINAL ARTICLE

Hepatitis E – A new era in understanding

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Abstract

Hepatitis E virus [HEV], the last of the five hepatotropic viruses to be discovered, was originally considered to cause an acute, travel-associated self-limiting illness restricted to humans; however, new research shows that there are animal reservoirs and zoonotic transmission. Additionally, HEV is now considered as a major health burden worldwide, leading to significant morbidity and mortality; therefore, the topic of hepatitis E is of re-emerging importance, having brought to light important questions such as the transmission of HEV, especially in developed countries, as well as treatment and vaccination options. HEV belongs to the genus *Hepevirus* in the *Hepeviridae* family. The HEV genome sequence is relatively stable; however, there is a diversity of genotypes which are helpful in comprehending the epidemiological phenomena. HEV is classified based on the nucleotide sequences of the genome and is now characterised as a single serotype with four major genotypes [HEV 1–4]. Hepatitis E cases are not clinically distinguishable from other types of acute viral hepatitis, although diagnosis can be strongly suspected in certain epidemiological settings. It is imperative to raise awareness among physicians about the importance of HEV, with the aim of helping recognise, prevent and treat HEV infections. This review article highlights the current developments of HEV in microbiology, epidemiology, clinical features, treatment and prophylaxis.

Key words

hepatitis E, genotypes, epidemiology, prophylaxis, antiviral therapy

INTRODUCTION

Although hepatitis E was initially documented as a novel disease in 1980, it was only in the early 1990s that the first case of hepatitis E was identified and sequenced [1]. Hepatitis E Virus [HEV] was the last of five hepatotropic viruses to be discovered [2]. HEV is now established as the key worldwide etiological agent of enterically-transmitted non-A, non-B hepatitis, and is accountable for more than a half of the cases of acute hepatitis in endemic countries [3]. Historically, due to the endemicity in developing countries, and the rational that HEV in developed countries occurs infrequently, namely, only on occasions when travellers visited endemic areas, HEV has not been given the due consideration it requires. Recent evidence now shows that there is an increase of HEV cases in developed countries, and more sporadic cases without a history of travel [4]. This review article offers an analysis of current data concerning microbiology, epidemiology, clinical features, treatment and prophylaxis of HEV.

Microbiology. HEV was first visualised in 1983 by using immunoelectron microscopy [5]. HEV belongs to the genus *Hepevirus*, in the *Hepeviridae* family, which is a positive-sense small [27–34 nm] single-stranded RNA non-enveloped virus with an icosahedral capsid. The virus has a 7.2 kb genome which contains three Open Reading Frames [ORFs]. ORF1 encodes 1,693 amino acids with domains for non-structural proteins of other positive-strand RNA viruses which include cysteine protease, methyltransferase, RNA helicase and RNA dependent RNA polymerase domains. ORF2 has three linear domains which consist of the shell domain (amino acid 129–319), middle domain (amino acid 320–455) and the last domain which includes the neutralizing epitopes called the protruding domain (amino acid 456 -606). ORF2 encodes the viral capsid protein of 660 amino acids, which is key to the virion assembly, communication with target cells and immunogenicity. ORF3 overlaps ORF2 at its 3' end by approximately 300nt, which is involved in virion morphogenesis and release. The virus replicates in the cytoplasm, with the sub-genomic RNA producing the ORF2 and ORF3 proteins, which serve as templates for replication [6, 7].

HEV is classified based on the nucleotide sequences of the genome and is now characterised as a single serotype with four major genotypes [HEV 1–4], with each genotype having several subtypes. Genotype 1 which has five subtypes (1a – 1e), has been isolated from both tropical and some subtropical countries in Asia and Africa. Genotype 2 that has two subtypes (2a and 2b), which have been isolated in: Mexico, Nigeria and Chad [8]. Genotype 3 which often affects the elderly with ten subtypes (3a – 3j), and have been found worldwide – Asia, Europe, Oceania, North and South America, and genotype 4 which has seven subtypes (4a – 4g) with limited isolation, mainly in Taiwan and China. The most frequently identified causative agent of hepatitis E in developing countries are genotypes 1 and 2, which are restricted to humans, and is especially associated with males, with larger outbreaks and epidemics in developing countries with poor sanitation, while genotypes 3 and 4 infect humans, pigs and other animals, and have been responsible for sporadic outbreaks in both industrialised and developing countries [9]. Table 1 summarises key points of each genotype.

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Table 1. Hepatitis E virus genotypes.

Characteristics	genotype 1	genotype 2	genotype 3	genotype 4
Geographic Location	Africa and Asia	Mexico, Nigeria and Chad	developed countries worldwide	China and Taiwan
Viral discovery	1983	1986	1995	2003
Subtypes	5	2	10	7
Transmission route	water-borne faecal-oral person to person	water-borne faecal-oral	food-borne	food-borne
Groups at high risk for infection	young adults (15–30)	young adults (15–30)	Adults aged over 50 and male immuno-compromised persons	young adults
Zoonotic transmission	no	no	yes	yes
Chronic Infection	no	no	yes	no
Outbreaks	common, can involve thousands of cases	smaller scale outbreaks	uncommon	uncommon
Transfusion related infection	yes	yes	yes	yes

Recent data based on the complete genome sequences from human and animal strains, as well as ORF1 and ORF2 amino acids sequences, indicate that there are three groups of mammalian HEV. The first group corresponds to viruses infecting humans, pigs, deer, wild boar and rabbits, the second group infects ferrets and rats, and the third group infects bats. It has been proposed that in the future there is a possibility for a new HEV nomenclature, with four genera that comprise of: *Avihepevirus*, including avian strains; *Chiropteranhepevirus*, including bat strains; O*rthohepevirus*, including mammalian strains except bat HEV; and *Piscihepevirus*, including cutthroat trout virus [10, 11].

New data has indicated that due to the improvement of water supplies and sanitary facilities, the major source of HEV infection is animals, with a new genetically different genotype of HEV having been recently detected in faecal samples of camels in the Middle East, as well as in farm rabbits in China, giving rise to the potential of additional genotypes [12, 13].

Epidemiology. Annually, HEV is thought to cause around 20 million infections, resulting in three million acute illnesses, and 57,000 deaths each year [14]. The earliest well-documented epidemic of HEV was in Delhi, India, during 1955–1956, which affected approximately 30,000 people; it was caused by the contamination of the drinking water supply with faecal matter. Initially, this epidemic was thought to be caused by HAV, however, after a backdated examination of the affiliated patient stored sera, it was discovered to be due to a new infectious agent – HEV. In Europe 5–15% of hepatitis patients are diagnosed with acute HEV. In Poland, 182 patient sera were tested for anti-HEV IgM and IgG, and 15.9 % were found to be positive for IgG and only three sera were reactive for IgM; the clinical course of HEV patients in Poland are largely asymptomatic. Zoonotic HEV transmission is considered to be the main source of infection in developed countries. In one study, HEV-specific antibodies were detected in 44.4% serum samples obtained from wild boar in Poland, showing that wild boar are an important reservoir of the virus. Another study examined the presence of HEV in pork sausages at points of sale in Spain, Italy and the UK, where 6%, 6% and 10% of HEV were detected, respectively. HEV was detected in 60% of samples taken from the areas of pig dissection slaughtering. A large study carried out from 2003–2012 in England and Wales showed that from a total of 2,713 diagnosed cases of hepatitis E, 1,376 were indigenous infections, with an evident increasing trend in indigenously acquired cases, which suggests the risk of acquiring HEV has changed. In Moldova, Eastern Europe, a study comparing swine farmers (264) and a control group without occupational exposure to swine (255) found a higher prevalence of 51.1% positive anti-HEV IgG in swine farmers compared to 24.7% in the control group, and it was noted that the swine farmers had an increased prevalence if they were over the age of 40.

During 1982, a researcher was successfully infected with HEV via oral administration of collective stool extracts from nine patients from a non-A, non-B hepatitis outbreak that occurred in a Soviet military camp located in Afghanistan. In developing countries, HEV is mainly transmitted via human faecal shedding through contaminated water, thus maintaining a circulating pool of infected individuals and sustains the disease in an endemic population. In endemic areas, sporadic cases may be caused by the transfusion of infected blood products, vertical transmission from a pregnant woman to her foetus, and the ingestion of raw or uncooked shellfish. In developed countries, animal reservoirs play an important role in most cases since they are largely locally acquired; commonly, domestic pigs are affected and remain asymptomatic. Zoonotic transmission of HEV may spread via the consumption of uncooked or undercooked infected pork and meat. Experts for the European Food Safety Authority Biohazard have acknowledged that additional studies on HEV circulation are essential to clarify farm-to-table risk assessments [22, 23].

The frequency of asymptomatic HEV infections has led to fears about transmission occurring via blood products. Recent cases of HEV transmission through blood products in the UK were discovered to be from indigenous viruses within genotype 3f, this has strengthened the theory [24]. Groups that could be involved in transmission through blood products are paid blood donors positive for other blood-borne viruses, and in multiple-transfused haemodialysis patients who have an increased number of HEV seroprevalence levels, potentially signifying that HEV could be acquired parenterally [25].

Clinical features. In the majority of patients, HEV causes a self-limiting illness which lasts a few weeks and can be asymptomatic, especially in children [26]. Following an initial two to six weeks incubation period, symptoms may start to develop with a primary phase consisting of mild fever, nausea, skin rashes or joint pain, followed by abdominal pain, vomiting, anorexia, malaise and hepatomegaly. 40% of patients are symptomatic with jaundice, along with dark urine and pale stools. Hepatomegally, a slightly enlarged tender liver may also occur [27].

Infrequently, acute hepatitis can be severe, leading to fulminant hepatitis which is also known as acute liver

failure. This is especially the case for those in the 3rd – 4th trimester of pregnancy, individuals with pre-existing chronic liver disease or experiencing alcohol abuse. These increase the patients' risk of death due to complications of hepatic encephalopathy and HEV-associated acute liver failure [28]. It has also been observed that individuals with acute and chronic HEV infections can develop many neurological manifestation which are shown in Table 2. In 126 patients with acute HEV, 5.5% developed neurological complications, and there were neurological signs and symptoms in 6% of solid organ transplant recipients with chronic HEV infection [29, 30]. In endemic countries, HEV mainly affects children and young adults, being more common in males with a mortality rate of 1–15%. This is in contrast to developed countries, where most individuals affected are over the age of 60, with a percentage of icteric hepatitis seemingly higher, hence giving a poorer prognosis [31]. Hepatitis E cases are not clinically distinguishable from other type of acute viral hepatitis; however, diagnosis can be strongly suspected in certain epidemiological settings. Acute viral hepatitis is indicated when serum aminotransferase levels are elevated in laboratory examinations – serum alanine aminotransferase (ALT) levels are more often higher than the serum alanine aminotransferase (AST) level. ALT, can be raised by ten to twenty times the upper limit of normal, increasing rapidly and peaking at four to six weeks from onset. ALT generally returns to normal within two months after the peak severity of the disease. Also, the serum alkaline phosphatase level may be normal or slightly increased (up to three times the upper limit), and serum bilirubin level usually ranges from 5–20 mg/dl, depending on the hepatocytes damage. There may be leukopenia, with lymphopenia or neutropenia. Hepatic failure is indicated if there is an increased prolonged prothrombin time longer than 16s, decreased albumin and very high bilirubin level; a liver transplant may be needed [32].

Table 2. Neurological manifestation of HEV infection

Neurological Manifestation	
Acute HEV infections	Chronic hepatitis E
"Guillain-Barré" syndrome	bilateral pyramidal syndrome
polyradiculoneuropathy	inflammatory polyradiculoneuropathy
bilateral brachial neuritis	peripheral neuropathy
peripheral neuralgia with meningitis	encephalitis
transverse myelitis	proximal myopathy
neuralgic amyotrophy	
seizure	
pseudotumour cerebri	
nerve palsies	

More precise diagnosis of hepatitis E infections are broadly classified into two types: direct and indirect. Direct methods for detecting the virus, viral proteins or nucleic acids in both the blood and stool samples by immune electron microscopy and reverse transcriptase polymerase chain reaction (RT-PCR). RT-PCR, is used in areas where hepatitis E is infrequent and with chronic HEV infection, as well as being used to determine the efficiency of treatment [33]. Indirect diagnosing methods detect the anti-HEV IgM and IgG antibodies. Anti-HEV IgM are detectable four days after the onset of jaundice and persists for from three to five months, with a peak at the onset of biochemical abnormalities/symptoms [34]. Using the enzyme-linked immunoassay (ELISA), detection of IgM antibodies presents a sensitivity of 72–79% and specificity of 78–98% problems; this is the best method for detecting and diagnosing acute hepatitis E infection, but there is only a short period of viraemia (two weeks in the serum and from four to twelve weeks in the stool). Therefore, an absence of HEV RNA does not exclude the diagnosis of acute hepatitis E [35].

In immunocompetent patients, acute hepatitis E is usually diagnosed by indirect methods; however, in immunocompromised patients, antibodies of HEV-RNA may appear late or not at all. RT-PCR is strongly recommended for diagnosis of immunocompromised patients [36].

Treatment. In most cases of immunocompetent patients with HEV infections, no treatment is needed since it normally clears spontaneously, and only occasionally needs symptomatic treatment; nevertheless, ribavirin can be given; a non-immunocompromised patient with severe acute HEV infection was treated with ribavirin (1,200mg/day) for twenty-one days, and showed that there was a significant improvement of liver function tests, normalised ALT with a decrease in bilirubinemia [37]. In a recent case study of 59 post-solid organ transplant patients with chronic hepatitis E who used a three months monotherapy of ribavirin, resulted in viraemia in 46 of the 59 [78%] patients [38]. Ribavirin therapy is contraindicated in pregnancy due to the teratogenicity of the drug, but the risk of untreated HEV to both the foetus and mother is high; therefore, antiviral therapy must be considered. As chronic hepatitis E (CHE) virus can rapidly progress to cirrhosis, therapeutic intervention should be considered in immunocompromised patients. The preferred method of treatment in a transplant recipient with CHE infection is via viral clearance; this can be first established by reducing the immunosuppressive therapy which generally results in a 30% viral clearance in patients, suggesting this potentially should be the first line therapeutic approach in CHE [20]. Drugs including Calcineurin inhibitors (cyclosporine A, tacrolimus) and mTOR inhibitors (rapamycin, everolimus) have an *in-vitro* effect of stimulation of HEV replication. Conversely, mycophenolic acid (including prodrugs mycophenolate mofetil) inhibits the HEV replication *in-vitro*. Steroids were found not to influence the HEV replication. In patients in which immunosuppressive therapy cannot be reduced, antiviral therapy should be considered, which can include ribavirin monotherapy (600–1,000mg/day) for at least three months. However, if there is a G1634 mutation in the RdRp domain of HEV ORF1 protein, there have been reports of treatment failure when using ribavirin, and in such cases pegylated interferon alfa may be used if there are no contraindications. Furthermore, electrolyte treatment may be needed in patients with dehydration or malnutrition, which could include potassium chloride, calcium gluconate and potassium phosphate [37].

Prophylaxis. Individuals infected by HEV and who recover will be protected due to CD4 and CD8 T cells. Another way to induce immunity is via vaccines; to date, 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 both safe

and had an efficacy of 95.5%, but due to hepatitis E infection, at the time being rare in developing countries, research was not continued due to the lack of profitability [39]. In 2007, a recombinant HEV vaccine was developed and tested on 2,000 healthy Nepalese males. After three doses, 95.5% of the patients developed anti-HEV antibodies [40].

The People's Republic of China has recently developed a vaccine, HEV 239, which is expressed in *Escherichia coli* and occurs as a virus-like particles of 23nm in diameter. It is a 26-kDa protein encoded by ORF2 of HEV vaccine [41]. In a phase II study piloted among seronegative adults, the vaccine was found to be safe, immunogenic, and provided protection against HEV infection with an efficacy of 83% [42]. A phase III trial in eleven cities in eastern China was conducted with half the participants being randomly-assigned to received three intramuscular injections of HEV 239 at 0.1 and six months, or a placebo or hepatitis B vaccine. They were followed-up to see the effects up to and including nineteen months later. The vaccine was well tolerated and protected against HEV with an efficacy of 100%. This vaccine is currently licenced only in the People's Republic of China [43].

Prophylaxis is the most effective approach which is accomplished by reducing exposure to the pathogen for HEV. However, the recommendations for prevention are difficult to make because although we are aware polluted food, especially pork and deer, have been considered the main mode of HEV3 transmission, other possible routes of infection have been pointed out, including unknown routes and sources [44]. Having good sanitation and accessibility of uncontaminated drinking water by the establishment of a proper disposal systems for human faeces helps prevent HEV; boiling and chlorination of water inactivates HEV. Also, maintaining good hand hygiene practices after using the restroom, and eschewing ice cubes is another preventative measure. HEV is thermally stable after heating to 56^0C for one hour; nevertheless, HEV can be inactivated when heated to 71^0C for twenty minutes [45], hence avoiding the consumption of uncooked meats, as well as the ingestion of raw pork and venison to decrease the possibility of an infection from HEV3. Another issue is blood donation in immunocompromised patients.

CONCLUSION

Today, with a fuller understanding of HEV, new questions and challenges arise. It is evident that HEV infection is a major global health burden which leads to significant morbidity and mortality, with zoonotic transmission being the major cause of transmission in developed countries. Therefore, tests for HEV should be considered if patients present with increased liver transaminase levels, especially those individuals who are pregnant or immunocompromised. Additionally, in view of the successful HEV 239 vaccine, it is worth considering providing the vaccine worldwide to healthy adults at risk of acquiring hepatitis E, such as travellers, after further studies have been conducted on the efficacy of HEV 239 in endemic regions, pregnant patients, and immunocompromised patients. Increased awareness among physicians about HEV is also the key to recognition, prevention and treatment.

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