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HEV: an underestimated hepatitis virus and its challenges

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Abstract
Hepatitis E is one of the major causes of acute viral hepatitis globally. It affects millions of people, leading to thousands of death every year. It was thought to be common in developing countries, however it has posed equal threat to developed nations in the near decades. Endemic regions experience waterborne epidemics usually, while sporadic cases in industrialized areas are mainly of zoonotic origin. Risk group persons include pregnant women, immunocompromised individuals, patients with chronic liver diseases, persons in close contact with HEV infected animals, infants and older people. Both acute and chronic infections are seen, along with a wide range of extra hepatic manifestations. A large number of cases undergo unrecognized or misdiagnosed due to inadequate knowledge and awareness of the disease. A combination of serological and nucleic acid amplification tests are recommended for the diagnosis of HEV infection. Ribavirin and Interferon – alpha are widely used for treatment, but with a limited success. Improvements in suspicion, recognition and diagnosis are necessary to decrease the burden of disease throughout the world.

Keywords: *HEV, Hepatitis, RNA virus, Fecal-oral, Zoonosis*

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I. Introduction

Hepatitis commonly refers to an inflammatory condition of the liver. Viral hepatitis is mainly caused by viruses like Hepatitis A, Hepatitis B , Hepatitis C, Hepatitis D, Hepatitis E and Hepatitis G viruses. Hepatitis E virus (HEV) spreads primarily through fecal-oral route via contaminated water. This is hyperendemic in regions having poor sanitization. However zoonotic cases of HEV has also been reported in the developed nations.[1] HEV is now the most common cause of acute hepatitis and has been associated with 20.1 million new cases in Asia and Africa annually, leading to 70000 deaths and 3000 still births.[2] Acute hepatitis is generally asymptomatic or mildly symptomatic in immunocompetent patients characterized by nausea, vomiting, fever, body aches and malaise, jaundice and dark coloured urine.[3] It can also cause severe infections in older people and in Acute-on-chronic liver failure patients. In both immunocompetent and immunocompromised patients it is also known to cause extrahepatic manifestations. It has a higher mortality in older age group, very young children and pregnant women. HEV has 8 genotypes,[4] 5 of which have known to cause infections in humans.[5,1,2]

II. Virology

HEV is a member of the family Hepeviridae, which belongs to genus Orthohepevirus. Orthohepevirus contains four species, A to D[6] . HEV is of the species Orthohepevirus A. Species A which causes diseases in humans has eight genotypes (HEV 1 – HEV 8)[4]. Two of these, HEV 1 and HEV 2 are obligate human pathogens. HEV3 and HEV 4 are found in several animals and cause zoonotic infections in humans. Genotype 5 and 6 are restricted to wild boars and Genotype 7 and 8 are found in camels. Genotype 7 was recently reported in a patient consuming camel milk and meat.[5]

HEV is an icosahedral, non-enveloped virus with size ranging from 27 - 34 nm. The virus has a positive sense single stranded RNA containing three partially overlapping open reading frames (ORFs). ORF 1 present at the 5' end is 1693 amino acids long and is responsible for coding nonstructural proteins involved in RNA replication like the RNA-dependent RNA polymerase and RNA helicase. ORF 2 present at the 3' end is 557 to 641 amino acids long and encodes the capsid. ORF 3 which overlaps ORF 2 and ORF 1 is responsible for the release of virus particle.[7] ORF 4 was recently discovered in HEV 1 and is thought to play a crucial role in the functioning of HEV 1 RNA polymerase.[8]

HEV was thought to be a non-enveloped virus based on the appearance of the virions isolated from faeces and bile, which are naked. However it was found that the virions in blood were wrapped in host cell membranes.[9] This process of becoming enveloped is not fully understood but ORF 3 appears to play a crucial

role.[10] It is thought that the envelope of the virions may be degraded by the action of bile, which results in non-enveloped virus in bile and faeces.[11] These quasi–envoloped virions don't have any surface antigen and are resistance to neutralizing effects of the major anti-HEV antibodies produced against ORF 2.[10] These quasi enveloped and non-enveloped viruses have different mechanisms of entering the host cells.[12]

It is thought that quasi-envelope may lend HEV, exosome- like properties[13] which allows the virus to enter immunologically privileged sites [CNS, testes][14] and a range of cell lines via an endocytic mechanism.[11]

III. Route Of Transmission And Epidemiology

Cases of HEV infection has increased significantly in the last decades. Genotype 1 and 2 are obligate human pathogens and spread primarily fecal-orally via contaminated water. This is hyperendemic in countries having poor sanitization, which includes several countries of southern Asia[15-17], parts of Africa[18] and rural China[19]. However, epidemics do not occur year after year in the same geographical area. Following an outbreak, the seroprevalence of IgG antibody against HEV increases by an average of five times in that area. Over the years there is a decline in the seroprevalance until a level where it does not offer herd immunity and another epidemic can occur.[20]

In a large outbreak in Uganda in 2007-2008, direct person to person transmission via the faecal-oral route was proposed to be the cause of the epidemic spread. This route of transmission is suggested to be linked with sporadic cases of HEV.[21,22]

Genotype 3 and 4 of HEV cause zoonotic infections. These genotypes are found in various species including wild boar,[23] deer[24] and rabbits[25], its primary host being pigs[26]. The virus being nonpathogenic[27] in pigs avoids the chances of easy detection. The consumption of meat of infected animal is thought to be the most important route of transmissions as suggested by isolation of virus from pork products.[28] These genotypes are also detected in feaces and milk of asymptomatic animals like cows.[29] However, some experiments suggest that the virus can be inactivated if heated at 71^0C for a minimum of 20 minutes.[30]

Transmission via infected blood and blood products from patients though rare is a possible route of transmission.[31] In a study in UK with 225000 blood donations it was revealed that 0.035% of recipients were viremic or developed antibodies against HEV.[32] However most of the transmission remain asymptomatic in an immunocompetent person. Routine testing for HEV in blood products is currently being done in Ireland, United Kingdom and Netherlands.[33]

In a study by Khurro et al., vertical transmission was first demonstrated in 5 out of 8 babies whose mother were infected during the third trimester.[34] In a separate study, Kumar et al. demonstrated that the transmission from infected mother to foetus was 100%.[35] Vertical transmission has a variety of complications including neonatal demise or intrauterine demise.[34]

HEV 1 and HEV 2 have been associated with 20.1 million new cases in Asia and Africa annually, with 3.4 million symptomatic cases, 70000 deaths linked to acute liver failure and around 3000 still births.[2] Genotype 1 is more prevalent in Asia and north Africa and Genotype 2 in Mexico and West Africa.

The seroprevalence of anti HEV antibodies in hyperendemic regions like Asia and Africa was found to be 10-40% with more frequency towards the older age group above 50 years.[36] This low rate can be attributed to disappearance of antibody with time or low sensitivity of tests used for detection of antibody.[37]

HEV 3 and HEV 4 are primarily found in more developed countries such as Japan, China, UK, France, US.[1] France was found hyperendemic to HEV 3 with a seroprevalence greater than 50% in the southwest region.[38] In a survey involving 30 countries of the Europe, the HEV infection had gone up from 514 in the year 2005 to 5617 in 2015.[39] The United States however reported a low seroprevalence of 6%.[40] This can be attributed to low organ meat consumption, lack of Food and Drug Administration licensing for any assay to detect infection and low awareness about HEV among the health systems.[37]

HEV 5 and HEV 6 have only been found in wild boars and are currently not associated with any human infections.[41]HEV 7 and HEV 8 have been found in camels,[42] however HEV 7 was also found in a liver transplant recipient patient in UAE in the year 2016 and was associated with regular consumption of camel milk and meat.[43]

IV. Clinical Picture

A. Acute infection (in immunocompetent host)

Acute hepatitis is generally asymptomatic or mildly symptomatic in immunocompetent patients. It is characterized by nausea, vomiting, fever, body aches and malaise, importantly by jaundice and dark coloured urine.[3] In general a more severe infection is seen in HEV 1 and HEV 2 as compared to HEV 3 and HEV 4.[44] However, HEV 3 and 4 may cause severe infections in older people and in Acute-on-chronic-liver failure patients.

In developing countries of Asia, Africa and Central America, only acute infections of HEV 1 and HEV 2 are reported. In developed countries, locally acquired infections are mostly caused by HEV 3 and HEV 4.[45]

During the year 2014 and 2015, UK, Germany and France reported more cases of acute HEV infections than acute HAV or HBV infections.[46] Older males are affected more than females with a ratio of 3:1, the median age group being 63 years.[47] The host factors are thought to play a role in this rather than any difference in exposure. Most patients present an acute self-limiting infection that last for 4 to 6 weeks.[48] Disease progression to liver failure is rare, but reported in few individuals in Europe and a single centre study in German reported 10% HEV infections among 80 patients with acute liver failure.[49] The overall mortality of the infection ranges from 0.2% to 4%,[37] but can be higher in those with pre-existing liver disease or very young children.

B. HEV in immunocompromised host

There has been no case to suggest chronic hepatitis by HEV 1 and HEV 2.[50,51] However, immunocompromised patients may not be able to clear HEV and develop chronic hepatitis, when infected by HEV 3 and HEV 4.[51,52] Kamar et al[50] has also suggested chronic infection in solid organ transplant recipient such as kidney or liver recipient for the first time in 2008. Patients who are viremic even after 3 months of onset of infection can be regarded as chronically infected. In a small number of HEV positive solid organ transplant recipient, clearance of HEV without specific treatment between 3 to 6 months was reported.[52]

Though most patients show no symptoms or only mildly elevated liver enzymes, fatigue is known to be the most common symptom.[53] 20-50% of transplant recipients who have exposure to HEV 3 develop chronic infection.[54] Chronic infection may lead to structural damage in the liver like nodule formation or subsequent cirrhosis.[55] In around 10% of patients with chronic HEV infection, cirrhosis develops within 2-5 years.[56] People who are at high risk of chronic infections includes individuals with AIDS,[57,58] those receiving immunosuppressive therapy[59] and patients with autoimmune disorders.

C. HEV in pregnancy

HEV infection caused by HEV 1 and HEV 2 in developing countries has a higher morbidity as compared to those caused by HEV 3 in the developed countries.[60] A possible explanation for this was provided by Gouilly et al[61], who demonstrated that HEV 1 proliferates more than HEV 3 ex vivo in tissue explants of fetal placenta and decidua basalis and in stromal cells. They also found increased cell death and necrosis at the maternal-fetal interface along with changes in structure of placental barrier in HEV 1 infection. HEV 1 also triggers production of cytokines like IL-6 and chemokines which may be associated with higher viral load and subsequently more tissue damage.[61]

Study shows HEV as a leading cause of acute viral hepatitis and acute liver failure in around 80.36% and 73.38% of cases respectively.[60] The mortality ranges from 15 to 25% for HEV 1 acquired during the third trimester.[62] Other complications such as cerebral edema and encephalopathy has also been associated with acute liver failure in 70% of HEV infected pregnant women.[63] There can be various fetal complications ranging from intrauterine death to neonatal deaths[64,65] in around 56% HEV infected pregnant women. [66]

D. Extrahepatic manifestations

Both acute and chronic infections of HEV may cause extrahepatic manifestations. This includes a wide range of conditions like neurological disorders,[67] glomerulonephritis, haematological and autoimmune disorders (myasthenia gravis,[68] schonlein purpura,[69] thyroiditis[70]) and acute pancreatitis.

In immunocompetent patients, cases of neurological injury have been reported. In all cases of neurological injury, LFTs are mildly affected and the neurological conditions such as Gullian-Barre syndrome(GBS) neuralgic amyotrophy(NA) and encephalitis dominate.[67] There have been reports of neurological injury in chronically infected patients also.

GBS which is characterized by rapid onset & progressive muscle weakness causing respiratory and autonomic dysfunctions is immune-mediated polyradiculopathy.[71]Antibodies produced against gangliosides through the mechanism of molecular mimicry after HEV infections are suggested to lead to GBS.[72] A Dutch study revealed that 5% of patients with GBS had HEV infection.[73]

In a short study with Anglo-Dutch patients, 10.6% of patients with NA were infected with HEV around the onset of symptoms.[74] NA is an acute monophasic neurological injury which affects the brachial plexus. It is typically presented as a sudden onset of unilateral pain in dominant upper limb followed by weakness and impairment in the limb.[75]

Both immunocompetent and immunocompromised patients have reported cases of HEV associated glomerular disease.[76–79] The mechanism by which HEV causes renal injury is unclear. However, cryoglobulinemia associated glomerulonephritis which is a common complication of HCV infection is thought to cause glomerular injury in HEV infection in a similar way. Except one case of HEV 1, all other cases of renal injury was associated with HEV 3 infection.[76] A total of 8 patients have reported glomerulonephritis including IgA-glomerulonephritis, membranoproliferative glomerulonephritis, membranous nephropathy and nephroangiosclerosis.

Thrombocytopenia is also associated with HEV infections but is generally not severe, hence does not require specific treatment.

V. Diagnosis

The incubation period of the virus usually ranges from 2 to 6 weeks.[80] There are direct and indirect methods of testing. The direct method detects HEV RNA or viral capsid antigens and the indirect methods are based on the human immune response to generate antibodies against the virus.

The ORF 2 encoded capsid proteins are highly immunogenic and trigger the formation of IgM antibodies. The IgM antibodies are formed around 4 weeks after the infection and are in a detectable level for a period of 6 months.[81] The IgG antibodies which also develop simultaneously last for years and is indicative of both recent and past infection.[81] In some HEV infected patients testing positive for RNA, both IgM and IgG can be found negative, limiting the utility of these tests.[82] The kits used for testing of antibodies show a higher sensitivity in immunocompetent patient as compared to the immunocompromised patients. The sensitivity of IgM and IgG detecting kits decreases from 80-90% to 85-87.5% and 80-90% to 15-45% in the immunocompromised patients respectively .[83] An immunochromatographic assay is also available for the detection of IgM antibodies having a sensitivity of 93% and specificity of 99.7% based on the data from a study in Nepal and Indonesia.[84]

The HEV RNA is detectable from the blood and stool of the infected patients in which virions are found upto 4 weeks in the blood and 6 weeks in the faeces.[85] Most commercially used assays detect HEV RNA based upon Nucleic acid amplification tests. These includes Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and loop mediated isothermal amplification.[86,87] The RT-PCR method which is based on amplification of mostly ORF 3 is highly sensitive.[88] The FDA has not approved any assay for the detection of HEV.

Another method of detecting HEV infection is through sandwich ELISA which detects the capsid antigen, with an estimated sensitivity of 91% and specificity of 100% .[89] This can be used for detection of infection for upto 4 weeks. The blood levels of capsid antigen declines with rise of IgM antibodies thus reducing the sensitivity.[90] However low cost, ease of testing and early detection makes this a preferable option.

The varied clinical manifestations of the infection makes the diagnosis difficult. With limited knowledge of the disease, at times even specialists confuse the HEV infection with other hepatic dysfunctions such as Drug induced liver injury (DILI). Studies have revealed that a large proportion of patients who have been diagnosed with DILI in fact have acute HEV infection.[91,92] It can be equally challenging to distinguish acute HEV from autoimmune hepatitis, with false positive serological assay due to formation of cross-reactive antibodies.

VI. Treatment

Most of the infections are self-limiting and patients recover with supportive treatment. However, some patients with chances of acute liver failure may require specific treatment. Antivirals have shown to improve conditions of patients in HBV and HCV infections.[93−95] In Asia and Europe, few HEV patients have been treated with antiviral Ribavirin.[96−99]

Ribavirin, which is a pro drug, acts as a guanosine analog and inhibits viral replication.[100,101] The RNA-dependent RNA polymerase lacks proofreading activity making the process of RNA replication prone to error.[102] This suggests that the virus are close to the error threshold which is incompatible to the original RNA.[103] Ribavirin increases the mutations, which in turn pushes the virus towards the threshold inducing extinction.[104−107] However, there are higher chances of mutations that offer resistance to the antiviral, cause hepatic failure, lead to progression into chronic infection and reduce immune reactivity.[104−108]

In HEV resistant Ribavirin infections, Sofosbuvir, an NS5B polymerase inhibitor, which was approved by FDA for treatment of HCV infection was also considered a treatment option.[109] Billioti et al[110] demonstrated that use of Sofosbuvir – Ribavirin combination in patients with acute HEV infection showed better viral clearance.

For chronic HEV infections, the first line of treatment should be reduction of immunosuppressive drugs, particularly those which target the T cells.[111,112] If the risk of reduction of these drugs does not outweight the risk of chronic infection, this might lead to HEV clearance in around 33% of the patients.[112] With patients still having an active infection Ribavirin may be beneficial. The duration of treatment mainly varies from 3-6 months.[113]

In a small numbers of chronically infected liver transplant recipients, pegylated interferon α (IFN – α) has been used.[114,115] Though, treatment with IFN – α for transplant recipients is not recommended due to increased chances of rejection, there are reports suggesting effective treatment with Ribavirin, IFN- α and their combination in patients with hematological malignancies[116-118] and AIDS patients[119,120].

VII. Prevention

In hyperendemic regions where the route of transmission is mainly fecal-oral through contaminated water, regular disinfection of water bodies is an effective prevention method.[121,122] In developed countries with cases of zoonotic infection, proper cooking of meat[123,124] and pasteurization of milk are important ways to prevent the infection. Pregnant women and immunocompromised individuals should take more care and avoid raw meat .[125]

VIII. Vaccine

In the year 2010, a vaccine based on the ORF 2 encoded protein was assessed for phase 3 trial in China.[126] No serious side effects of the vaccine were observed. This is designed to provide long term protection against HEV genotype.[127] However no other country has approved the use of this vaccine and its safety in elderly, pregnant women, immunosuppressed patients and children is still to be demonstrated.

IX. Conclusion

HEV is the leading cause of non-A, non-B enterically transmitted viral hepatitis in both developing and developed countries. The epidemiology of HEV has not yet been studied in many countries. Although most of the infections are asymptomatic and self – limiting, it imposes significant risk in high risk group of individuals. There is no randomized, control trial yet to support the efficacy of the commonly used drug i.e Ribavirin. There is no treatment option for HEV infection in pregnancy, which is worrisome for clinicians. It is an underdiagnosed disease with varied clinical presentation. Hence, further studies have to be carried out for the better understanding of the natural course of the disease, diagnosis and management.

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