HEPATITIS E IN EUROPE: DIAGNOSIS AND TREATMENT

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Disclosure: The authors have declared no conflicts of interest.
Received: 22.05.15 **Accepted:** 29.09.15
Citation: EMJ Gastroenterol. 2015;4[1]:121-127.

ABSTRACT

Hepatitis E virus (HEV) is a single-stranded, non-enveloped, positive-stranded RNA virus that can be classified into four genotypes with distinct geographical distributions. Several reservoirs and transmission routes have been identified. The clinical symptoms of acute hepatitis caused by the different genotypes cannot be distinguished from each other and are similar to those caused by other types of hepatitis. In developed countries, fulminant hepatitis can develop in patients with underlying (liver) disease. Chronic HEV infections are reported in immunocompromised patients and can eventually result in fibrosis and even cirrhosis. Due to the nonspecific presentation, HEV infection is often misdiagnosed. Extrahepatic manifestations, mainly neurological syndromes and renal injury, have been reported. HEV infection can be diagnosed either by serological testing or by detecting HEV RNA in serum or faeces. Acute infections normally do not require treatment, but chronic infections should be treated by reducing immunosuppressive drugs, if possible, and/or using antiviral therapy. Recently, the efficacy and safety of an HEV vaccine has been studied. This review gives an overview of the current knowledge about the virus as well as the different clinical presentations, differential diagnoses, diagnostic strategies, and treatments of this infection.

Keywords: Chronic disease, hepatitis E virus (HEV), pigs, ribavirin, solid-organ transplant, zoonosis.

HEV: GEOGRAPHICAL DISTRIBUTION AND GENOTYPES

Hepatitis E virus (HEV) was discovered in 1983 after an outbreak of unexplained, non-A, non-B hepatitis at a military camp in Afghanistan.[1] It is a positive-sense, single-stranded, non-enveloped RNA virus that belongs to the genus hepevirus in the hepeviridae family. The virus consists of four genotypes with distinct geographical distributions, and all four of which can be harmful to humans. Genotypes 1 and 2 are restricted to humans, with HEV-1 found in Asia and Africa and HEV-2 found in Mexico, Nigeria, and Chad;[2] HEV is the most common cause of acute viral hepatitis in these countries.[3] Genotypes 3 and 4 can infect humans and other mammalian species such as swine, deer, rats, and mongooses.[4] These species act as potential hosts for the virus and it can be transmitted to humans by consumption of infected animals. In pig farming regions, and within herds of domestic swine, HEV prevalences of >60% have been reported.[5] Autochthonous HEV infections in Europe, the USA, and Asia are caused by genotypes 3 and 4.

Transmission of HEV Genotypes 1 and 2

HEV-1 and HEV-2 are found in developing countries with poor hygiene. The viruses are mainly transmitted by contaminated drinking water via the faecal–oral route and large outbreaks of acute hepatitis are reported.

Transmission of HEV Genotypes 3 and 4

Faecal–oral transmission of HEV-3 is reported repeatedly in pigs and swine and is considered to represent the greatest contribution to transmission within these species.[6] Over the past few years,

several HEV cases in humans have been reported to be due to the consumption of contaminated food products. The infections were linked to the consumption of undercooked pork, game, pig liver products, and shellfish.[4] It has been estimated that HEV shed in faeces from pigs and swine indirectly leads to the contamination of irrigation and drinking water via application of manure to land, and in this way can lead to the pollution of vegetables, fruit, and shellfish.[5,7]

In developed countries, cases involving transfusion-transmitted HEV infection have been reported.[8,9] In all of these cases, the donors were infected by non-travel-associated HEV genotypes. Studies on plasma pools testing positive for HEV RNA show that blood donors are often infected with HEV without having any complaints.[10,11] Seroprevalences of HEV in Europe are nationally and even regionally varied, ranging from the lowest recorded prevalence of 4.7% among Scottish blood donors[12] to 26.7% in the Netherlands[11] and even 53% in the south-east region of France, which is the area with the highest seroprevalence among industrialised countries.[13] When we compare these data with the recorded incidence of clinically evident autochthonous HEV infection in these countries, a large subclinical or unrecognised course of infection is suggested for transfusion-related HEV infection. A recent study in south-east England shows the risk and potential dangers of transfusion-transmitted HEV in immunosuppressed patients: these infections sometimes cause long-term persistent infections and can even lead to progressive chronic liver disease.[14]

A recent case report from Germany describes a male patient who was infected with HEV by liver transplantation. The patient received an HEV-infected liver from a donor with occult HEV infection. Shortly before explantation, the patient tested negative for HEV RNA and anti-HEV antibodies. One hundred and fifty days after transplantation, serology and HEV RNA were positive. Liver cirrhosis developed within 15 months and the patient died of septic shock.[15]

CLINICAL COURSE

Acute Hepatitis

Approximately half of all patients infected with HEV-1 or HEV-2 develop clinical symptoms of the infection, whereas 67–98% of patients infected with HEV-3 or HEV-4 remain asymptomatic.[4] The clinical features of acute HEV infection caused by the different genotypes cannot be distinguished from each other. In symptomatic patients, symptoms appear after an incubation period of 2–8 weeks.[16] Patients may present with unspecific complaints such as malaise, nausea, abdominal pain, vomiting, and anorexia. At presentation, patients can have fever and 40% present with jaundice.[17] During physical examination, right upper quadrant tenderness and hepatomegaly may be found. Laboratory findings show an increase in alanine aminotransferase (ALT) more than aspartate aminotransferase, as well as elevated bilirubin, alkaline phosphatase, and gamma-glutamyltranspeptidase.[18] ALT levels are sometimes normal during the period of viraemia.[19]

In highly endemic regions where patients are infected with HEV-1 or HEV-2, symptoms are most frequently observed in youths and adults.[20] In these areas, pregnant women have an especially greater risk of developing a more severe, acute liver disease that can lead to fulminant hepatic failure and even death.[21] It is suggested that this is due to differences in hormonal and immunological factors.[21,22] This epidemiological picture in pregnant women has not been observed in developed countries with predominant infection with HEV-3.

In developed countries, immunocompetent individuals without underlying diseases rarely present with symptoms. Studies into seroprevalence among blood donors underline the fact that patients are often silently infected.[10,23] Patients with symptoms are most often middle-aged and elderly males. The reason(s) for these associations are not fully understood. One explanation might be that all individuals are evenly exposed to HEV but that older patients have more significant comorbidities than young individuals and that this results in symptomatic HEV.[24] Alcohol consumption is also an important risk factor in the clinical expression of the infection. Consumption of at least 22 units of alcohol per week is strongly associated with symptomatic HEV.[25]

Several studies have shown that patients with underlying liver diseases have a poor prognosis when infected with HEV.[26] HEV infection in these patients can cause liver decompensation and acute-on-chronic liver failure.[27] One-year mortality rates of up to 70% have been reported.[4]

Chronic Infection

Chronic HEV infections, defined as the presence of HEV RNA in serum or stools for >6 months, are rarely seen in otherwise healthy patients but are increasingly being reported in immunosuppressed patients. Patients receiving solid-organ transplants (SOTs) require lifelong immunosuppressive therapy to prevent graft rejection and are prone to developing chronic HEV due to their suppressed immune system.[28] Since 2008, increasing numbers of chronic HEV infections have been reported in patients with liver, kidney, and heart transplants.[4] A recent study showed that predictive factors associated with chronic HEV infection were the depth of immunosuppression, the use of tacrolimus rather than cyclosporine A, low platelet and serum creatinine count at diagnosis, and low CD2, CD3, and CD4-positive cell counts.[29] In addition, mTOR inhibitors such as rapamycin and everolimus have a direct stimulatory effect on HEV replication by blocking the antiviral signalling pathway.[30] However, mycophenolate mofetil has been shown to have a protective effect in the clearance of HEV *in vitro*.[31] Mycophenolate mofetil probably exerts antiviral effects by inhibiting inosine monophosphate dehydrogenase, an enzyme that is important for RNA synthesis.[31]

In SOT patients it has been observed that viral clearance is either achieved within 3 months after infection or after 6 months and later. This implies that, in SOT patients, a chronic HEV infection can be defined as persisting HEV replication beyond 3 months after infection.[32] Approximately 60% of SOT recipients exposed to HEV develop a chronic infection.[29] Recipients of allogeneic hematopoietic stem cell transplantation (alloHSCT) are also at risk of developing chronic HEV due to insufficient lymphocyte recovery and the use of immunosuppressive therapy.[28,33] Studies into the seroprevalence of HEV among patients infected with HIV report conflicting results. Studies in Spain report a higher seroprevalence in patients infected with HIV,[34,35] whereas other reports found a similar seroprevalence in HIV-infected and control groups.[36-38] Chronic infections are rarely observed in HIV-infected patients, which may be explained by a high coverage of combined antiretroviral therapy in HIV-infected patients preventing a strongly decreased immune response.[16,36]

Patients with cancer who receive radiation therapy and/or immunosuppressive drugs are prone to develop clinical features of acute HEV infection, but usually recover completely following cessation of immunosuppressive treatment.[28] Chronic HEV infection can eventually progress to fibrosis and even cirrhosis, which can lead to death due to liver decompensation.[29,39,40] Cirrhosis due to chronic HEV sometimes requires re-transplantation in liver transplant recipients. These patients are at high risk of developing a recurrent infection if viral clearance is not achieved before transplantation.[40] No chronic infections with HEV-1 or HEV-2 have been reported in the literature.

HEV INFECTION MIMICS OTHER CONDITIONS

Drug-induced liver injury (DILI) is common and occurs frequently in the elderly population, as does autochthonous HEV infection. The clinical presentation of DILI is diverse and nonspecific. In order to effectively diagnose DILI, there needs to be a temporal relationship between the onset of drug therapy and biochemical evidence of liver injury. After inducing treatment with chemotherapy or other immunosuppressive drugs, infection with HEV can become symptomatic and may easily be mistaken for DILI. In fact, a study among patients with criterion-referenced liver injury showed that 13% of the patients who met the criteria had autochthonous HEV infection.[41]

In alloHSCT recipients, liver dysfunction related to graft-versus-host disease (GvHD) is common. A retrospective cohort study comprising 328 alloHSCT patients showed an incidence of 2.4% for HEV infections following transplantation.[33] The presentation of liver enzyme abnormalities in these two conditions are overlapping. It is important to differentiate HEV infection from GvHD because of opposing therapeutic strategies: increment of immunosuppression in GvHD versus reduction of immunosuppression in HEV infection.

The elevation of serum transaminase levels in HEV infection is also difficult to distinguish from patients with acute liver transplant rejection. Histological features of HEV include both cholestatic and classic types of acute viral hepatitis. However, lymphocytic destructive cholangitis has also been described, which can also be seen in primary sclerosing cholangitis, drug-induced hepatitis, acute rejection, and GvHD.[42] This makes it difficult to differentiate HEV from these diseases.[43] Until now, no specific HEV-related tissue markers have been available.

EXTRAHEPATIC MANIFESTATIONS OF HEV

Neurological manifestations have been reported in both HEV-1 and HEV-3 infections. Guillain–Barré syndrome and brachial neuritis are most frequently described.[44] Other neurological disorders include transverse myelitis, cranial nerve palsies (Bell's palsy), seizure, intracranial hypertension, acute meningoencephalitis, and neuralgic amyotrophy.[4,44] Impaired renal function has also been linked with HEV infection. Both HEV-1 and HEV-3 can cause glomerular disease. A study of HEV-related glomerulonephritis in SOT patients found that the majority of patients had cryoglobulinaemia, which became negative after HEV clearance. This leads to the hypothesis that cryoglobulinaemia plays an important role in HEV-associated renal injury.[45]

DIAGNOSTICS

HEV infection can be diagnosed either indirectly by the demonstration of anti-HEV antibodies or directly by detecting HEV RNA using a (quantitative) reverse transcription polymerase chain reaction ([q]RT-PCR) in serum/EDTA-plasma or stool samples.[46] After an incubation period of 2–8 weeks, HEV-specific immunoglobulin (Ig)M usually becomes detectable in immunocompetent individuals. At the time of clinical presentation, HEV IgM has already peaked and persists in blood for 8 weeks. Huang et al.[47] found that anti-HEV IgG can be detected in all HEV-infected patients, and in 95% of patients it is already present at the time of first presentation. Anti-HEV IgG reaches peak levels at around 4 weeks after onset of symptoms, and stays positive in high levels for >1 year.[47]

The presence of anti-HEV IgM antibodies represents an acute HEV infection in immunocompetent patients and is used as a marker for acute HEV infections. The presence of anti-HEV IgG alone is a marker of past infection. However, patients can also be re-infected with HEV. This is represented by a rapid increase in IgG titres, with HEV RNA becoming detectable by RT-PCR.

There has been poor correlation between the results of some immunoassays for the detection of anti-HEV IgM/IgG in terms of sensitivity, specificity, and agreement of results. Specificity levels range from 78.2–95.6% and sensitivity levels range from 72–98%, depending on the assay used;[48] the Wantai test is frequently used in Europe but was not evaluated in this study. We found that this assay is more specific (specificity: >99%; sensitivity: 75%)[49] than the tests investigated by Drobeniuc et al.[48] Our study also showed that, even though most assays are based on the detection of antibodies directed against HEV-1, there is major cross-reactivity against HEV-3, confirming that there is one serotype of HEV and contradicting earlier speculations that this may be the cause of the lower sensitivities of HEV-1 based immunoassays.

Due to the impaired immune responses and bad performance of IgM assays in immunocompromised patients, it is recommended to use real-time RT-PCR to detect HEV RNA in these patients. The virus is detectable in the blood of immunocompetent patients during the incubation period and in the early symptomatic phase, and in faeces 1 week before the onset of clinical signs.[50] A few days to weeks after the onset of clinical symptoms, HEV RNA is cleared from the blood; however, the virus continues to be shed in stools for another 2 weeks.[51] In patients developing chronic HEV infection, HEV RNA in serum remains detectable. Real-time qRT-PCR is also useful for monitoring treatment efficacy.

TREATMENT

In immunocompetent patients, acute HEV infection does not normally require treatment. There is one report describing the treatment of a 61-year-old man who had severe acute HEV-3 infection, which was treated with ribavirin. Liver inflammation rapidly improved concurrently with a decrease in HEV RNA levels after starting treatment. Prospective studies are needed to evaluate the role of treatment with ribavirin in patients with severe acute HEV infection.[52]

SOT patients treated with immunosuppressants to prevent rejection are at high risk of developing chronic HEV infection. Besides their primary inhibition of T cell proliferation, immunosuppressants can also affect the function of other types of immune cells, including B cells, dendritic cells, and natural killer cells. Suppression of the immune response in this way prevents the elimination of viral infections.[53] Given the strong association between immunosuppressant use and chronic HEV infection, dose reduction or even withdrawal of immunosuppression, if possible, is considered to be the first step in the treatment of HEV infection. In a retrospective study among 85 SOT recipients infected with HEV, nearly one-third achieved viral clearance after immunosuppressant dose reduction alone.[29]

Reduction of immunosuppressive therapy targeting T cells, such as cyclosporine A and tacrolimus, has a particularly great impact.[29] However, in heart and lung transplants this strategy should be considered with more caution given the difficulty in monitoring rejection in these patients.

In patients who fail to eliminate the virus after reduction of immunosuppressive drugs, and in those whose dose of immunosuppressive drugs cannot be reduced, antiviral therapy should be considered. Antiviral therapy consists of the off-label use of pegylated interferon alpha or ribavirin therapy, or a combination of both. Pegylated interferon therapy has been reported in a couple of studies with small populations consisting of 1–3 patients.[54-56] A 3-month course of pegylated interferon therapy showed sustained HEV clearance in two liver transplant patients[54] and one haemodialysis patient.[55] In one liver transplant recipient there was a relapse after completion of treatment. A 12-month course of pegylated interferon therapy showed sustained viral clearance in one patient.[56] However, interferon therapy cannot be used in patients with heart, kidney, and lung transplantation due to the increased risk of acute rejection. For these patients, and for patients with chronic HEV who are not able to clear the virus, ribavirin seems to be an efficient treatment option.

The largest study evaluating the effect of ribavirin therapy in SOT patients was conducted among 59 patients in France.[57] Kamar et al.[57] found an overall sustained virological response (SVR) in 78% of the patients. Six of the ten patients who had a recurrence were retreated, with four of them having an SVR after completing the second course of ribavirin. Ribavirin was administered for a median of 3 months and there was no difference in the overall rate of SVR between patients who received ribavirin for ≤3 months and those who received it for >3 months. Therefore, the authors suggest that ribavirin therapy for a duration of 3 months is sufficient.[57] The main side effects of ribavirin were anaemia and impaired renal function. Debing et al.[58] detected a mutation in the viral polymerase encoded by the HEV RNA of two non-responders to ribavirin treatment. This G1634R mutation seems to increase the replicative capacity of HEV in the liver and in this way reduces the efficacy of ribavirin.[58] Future studies are needed to investigate the clinical importance of this mutation in relation to other patient and virus-related factors in therapy resistance.

VACCINATION

Since rapid diagnostic tests for HEV infections are not yet readily available in most countries, a safe and effective vaccine is highly desirable. Currently, two vaccines against HEV seem to be effective: the recombinant protein (rHEV) vaccine and the HEV239 vaccine. The safety and efficacy of the rHEV vaccine was evaluated in a Phase II study among healthy, seronegative adults in Nepal. After two doses the vaccine efficacy was 85.7%, and was 95.5% after three doses.[59] However, the vaccine's production and further clinical trials were stopped due to economic reasons. The HEV239 vaccine showed a slightly higher vaccination efficacy. The vaccine was administered to 112,604 individuals, both seronegative and seropositive, in a Phase III trial. After three doses the vaccine efficacy was 100%. The vaccine was effective against HEV-1 and HEV-4.[60] A long-term follow-up study concerning this vaccine showed an efficacy of 86.8% after 4.5 years.[61] The HEV239 vaccine has also recently been shown to be highly immunogenic in rabbits.[62] These findings make it conceivable to study the effectiveness of this vaccine in preventing HEV transmission in pig populations and to tackle the problem at the source. However, this vaccine is currently only available in China and has not been introduced in Europe yet. Future studies are required to determine the efficacy of these vaccines against HEV-3 and their safety among immunocompromised patients and patients with chronic liver disease.

FUTURE PERSPECTIVES

In developing countries, improvement in sanitary hygiene is the most important way to control the faecal–oral transmission of HEV. In industrialised countries, the main source of the infection is from domestic swine, and its impact is highest in immunocompromised patients. Future studies are needed to investigate the best approach to the problem, either through primary prevention by tackling HEV at the source and/or through secondary prevention by vaccinating high-risk patients.

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