

Chronic hepatitis E: A brief review

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Abstract

Hepatitis E viral infection has traditionally been considered an acute, self-limited, water borne disease similar to hepatitis A, endemic to developing countries. However, over the past decade, zoonotic transmission and progression to chronicity in human patients has been identified, resulting in persistently elevated transaminase levels, progressive liver injury and cirrhosis. In addition to liver injury, neurological, renal and rheumatological manifestations have also been reported. Chronic hepatitis E occurs mainly in immunosuppressed individuals such as transplant recipients, human immunodeficiency virus patients with low CD4 counts and in patients with hematological malignancies receiving chemotherapy. Diagnosis is established by persistent elevation of hepatitis E virus RNA in the stool or serum. This population often requires treatment with antiviral agents, particularly ribavirin, as spontaneous clearance with reduction in immunosuppression occurs only in about a third of the patients. The purpose of this review, is to further discuss the clinical presentation, and recent advances in diagnosis, treatment and prophylaxis of chronic hepatitis E.

Key words: Hepatitis E virus; Chronic liver disease; Solid organ transplantation; Hematological malignancies; Immunosuppression

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Core tip: Chronic hepatitis E occurs mainly in immunosuppressed individuals such as transplant recipients, human immunodeficiency virus patients with low CD4 counts and in patients with hematological malignancies receiving chemotherapy. A few cases have also been reported in immunocompetent individuals. These patients may present with unexplained elevation in transaminases or less frequently with neurological or renal manifestations. The diagnosis is confirmed by a persistent elevation of hepatitis E RNA in serum or stool. Reduction of immunosuppression to achieve

spontaneous viral clearance should be attempted. However it is effective only in about a third of patients, therefore most patients require treatment with antiviral agents, like ribavirin. The purpose of this review is to increase awareness amongst physicians of chronic hepatitis E infection as a possible treatable cause of chronic liver disease, especially in immunosuppressed individuals.

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INTRODUCTION

Hepatitis E viral infection has traditionally been considered an acute, self-limited disease similar to hepatitis A. Over the past decade, progression to chronicity in human patients has been identified, resulting in persistently elevated transaminase levels, progressive liver injury and cirrhosis. In addition to liver injury, certain extra-hepatic manifestations have also been reported. Chronic hepatitis E occurs mainly in immunosuppressed individuals such as transplant recipients, human immunodeficiency virus (HIV) patients with low CD4 count and in patients with hematological malignancies receiving chemotherapy though a few cases have also been reported in immunocompetent individuals. While reduction of immunosuppression can lead to clearance of hepatitis E in one third of patients, treatment with antiviral agents, particularly ribavirin has shown promising results. The purpose of this review, is to further discuss the clinical presentation, and recent advances in diagnosis, treatment and prophylaxis of chronic hepatitis E.

VIROLOGY, EPIDEMIOLOGY AND TRANSMISSION

Hepatitis E virus (HEV) is a non-enveloped, single stranded RNA virus, 27 to 34 nm in diameter. It belongs to the family Hepeviridae. Five genotypes of HEV have been described of which genotypes 1 to 4 infect humans, while genotype 5 has only been known to infect birds^[1]. More recently, a new taxonomic scheme for the classification of HEV has been proposed based on analysis of existing genomic sequences^[2]. The hepatitis E virus belongs to the species orthohepevirus A, from the genus Orthohepevirus which includes isolates from human, mammalian and avian HEV^[2]. There are no known animal reservoirs for HEV genotypes 1 and 2 but genotype 3 can also affect animals such as deer, pigs, rodents, mongeese and shellfish^[1]. Genotype 1 and 2 infections are frequent in endemic regions such as Southern Asia, Africa and Mexico and are responsible for large waterborne epidemics in these areas^[3]. Genotype

3 was first identified in few sporadic cases in United States in 1997 and is now considered as a re-emerging zoonotic disease in several countries in Europe, North America and Japan^[4]. Genotype 4 has been reported to cause sporadic cases of acute hepatitis E in humans. These were previously thought to be restricted to Asia (China, Taiwan, Japan and Vietnam)^[3,4]. However, recent reports have identified autochthonous HEV genotype 4 infections in humans in Europe^[5].

The estimated incidence of acute HEV infection is about 3 million human infections per year worldwide resulting in about 70000 deaths^[6]. Most of these patients are in the endemic regions, but increasingly human infections, mainly from HEV genotype 3, are being reported in industrialized countries. HEV is transmitted predominantly by the fecal-oral route in the endemic areas. In the non-endemic areas, the mode of spread of HEV is food borne, especially from undercooked pork or infected raw meat from deer^[7,8]. The first evidence of a zoonotic source of autochthonous (locally-acquired) hepatitis E infection was reported from the United States when HEV isolates from humans were related closely to swine isolates^[9,10]. Subsequent data have corroborated this finding and therefore zoonotic transmission might be an important mode of spread of hepatitis E in the developed world. Person to person transmission is considered uncommon during both epidemic and sporadic setting^[11,12]. Vertical transmission from mother to fetus and blood transfusion related transmission of HEV has also been documented^[13,14].

Hepatitis E seroprevalence is high in developing countries like India and in Southeast Asia ranging from 27%-80% in the general population^[15]. Surprisingly, some studies from developed countries like United States and United Kingdom have shown an unexpectedly high seroprevalence of 21% and 25% respectively^[16,17]. The reasons for this high seroprevalence could be due to subclinical infection, exposure to animals, serological cross reactivity with other agents or false positive results. In particular, individuals coming in contact with swine, like veterinarians, pig breeders and slaughter house personnel have been found to have statistically significant higher rates of hepatitis E seropositivity in developed countries^[18-22].

The most common form of HEV infection is acute, icteric hepatitis which is self limited. The illness usually lasts for a few weeks and is followed by spontaneous resolution. Few patients have severe illness leading to fulminant hepatic failure. The mortality rate from acute hepatitis E ranges from 1% to 4%, though the risk of mortality is higher in pregnant patients and patients who are immunocompromised^[4].

DIAGNOSIS AND CLINICAL PRESENTATION OF CHRONIC HEPATITIS E

Diagnostic tests for hepatitis E can be classified as

indirect and direct tests. Indirect tests to diagnose HEV involves the detection of anti-HEV antibodies IgM and IgG in the blood. Direct methods involve detection of the virus itself or its constituents such as the viral nucleic acids^[23].

Anti-HEV IgM antibody is a marker of recent infection. It appears in the serum within a few days following infection with HEV and usually remains in the serum for about 3-6 mo. Anti-HEV IgG antibody is a marker of recent or remote exposure to HEV. It appears few days to weeks after the development of anti-HEV IgM, but lasts for a longer period of time. The titers of anti-HEV IgG gradually decrease with time and may eventually disappear. Diagnosis of acute hepatitis E is usually made by indirect tests. A positive anti-HEV IgM with or without a positive anti-HEV IgG confirms acute hepatitis E. A positive anti-HEV IgG in the absence of anti-HEV IgM suggests remote infection with HEV. It must be noted that testing for antibodies is unreliable in immunocompromised individuals, as they may not develop antibodies.

Chronic hepatitis E is diagnosed by detecting HEV RNA in the stool or serum by means of the direct viral nucleic acid tests^[23]. Viral nucleic acids can be detected in the blood and stool by using either reverse transcriptase-polymerase chain reaction (RT-PCR) or loop mediated isothermal amplification. The RT-PCR test is commonly used test for diagnosing chronic HEV. A positive RT-PCR after a minimum of 3-6 mo from the time of diagnosis of HEV, establishes the presence of chronic HEV^[24-26]. This is because spontaneous clearance may occur within the first 6 mo as noted in initial follow-up studies in immunosuppressed patients with positive HEV RNA^[22,23]. However, recently^[24], Kamar *et al.*^[24] reported that in transplant recipients who acquired HEV infection, none of the patients cleared the virus between 3 and 6 mo. The authors therefore suggested that in this population, persistence of HEV RNA in serum or stool beyond 3 mo should be considered as chronic hepatitis. It should be noted though that there is a wide variation in sensitivity of various assays for detection of HEV RNA^[27]. HEV genotype detected by one assay may not be detected by another assay and vice versa. Antibody tests are not useful in the diagnosis of chronic HEV. Presence or absence of serum anti-HEV IgG or IgM does not rule in or rule out chronic HEV. However, if a patient is noted to have anti-HEV IgG in the serum, testing for HEV RNA should be performed to detect underlying chronic HEV.

Chronic hepatitis E has almost exclusively been reported with genotype 3^[28], however a recent case study reports persistent hepatitis E in a child with HEV genotype 4^[29]. The source of infection in immunocompromised patients is often unknown but thought to be ingestion of pork or deer in most cases. In a retrospective study of 85 transplant recipients who got infected with hepatitis E, 32% were symptomatic at the time of diagnosis of HEV infection^[30]. Most common

symptom was fatigue (24%), followed by diarrhea (6%) and arthralgia (5%). Abdominal pain was present in 3% patients while jaundice was seen in only one patient. Fifty-six out of 85 patients (66%) developed chronic hepatitis while the infection resolved in the remaining patients without any specific intervention. On univariate analysis, aspartate transaminase and alanine transaminase (ALT) levels at the time of diagnosis and peak levels for these enzymes were significantly lower in patients who progressed to chronic hepatitis. The ALT elevation in chronic hepatitis E is modest (usually less than 300 IU/L) as compared to acute hepatitis E (more than 1000 IU/L)^[28]. While chronic hepatitis E can lead to spontaneous resolution in some patients without any specific intervention, it can lead to rapid progression to cirrhosis and death in others^[25]. There is no correlation between serum HEV concentration and progression to liver fibrosis^[31].

EXTRA HEPATIC MANIFESTATIONS OF CHRONIC HEPATITIS E

Several extra-hepatic manifestations have been described in patients with HEV infection, in both acute and chronic phases. Neurologic complications are the most frequent extra-hepatic manifestations. In a study of 126 patients with acute and chronic HEV infection, 7 (5.5%) patients had neurologic manifestations^[32]. Four of these patients were immunocompromised and had chronic HEV infection; 3 had received solid organ transplant, while one patient had HIV infection. Bilateral pyramidal signs, ataxia, proximal myopathy, encephalitis, cognitive dysfunction, peripheral demyelinating polyneuropathy, painful sensory peripheral neuropathy were the wide range of neurologic manifestations noted in these immunocompromised patients with chronic HEV infection. HEV RNA was detected in the cerebrospinal fluid in all 4 patients with chronic HEV infection. Neurologic symptoms either completely resolved or significantly improved in all patients who achieved viral clearance with treatment for HEV. The mechanism and pathogenesis of neurologic manifestations in patients with HEV infection is as yet unclear.

Renal complications have also been reported in patients with HEV infection. Membranoproliferative glomerulonephritis and relapses in IgA nephropathy were noted in solid organ transplant recipients with acute and chronic HEV infection^[33]. Cryoglobulinemia was also noted in 70% of these patients, with complete resolution following therapy with ribavirin. A case of membranous glomerulonephritis associated with chronic HEV infection in a kidney transplant recipient has also been reported^[34]. Nephrotic syndrome improved after the introduction of ribavirin, and completely resolved after the clearance of the virus.

Rheumatologic manifestations such as arthralgia, myalgia, skin rashes and cryoglobulinemia have been

reported in chronic HEV infection^[35].

CHRONIC HEPATITIS E IN SOLID ORGAN TRANSPLANT RECIPIENTS

Kamar *et al*^[24] in 2008 reported 14 cases of acute hepatitis E following solid organ transplantation out of which 8 progressed to chronic hepatitis. All patients with chronic HEV had a cadaveric transplant (kidney and liver transplant was done in 3 patients each while 2 patients underwent combined kidney and pancreas transplant). Since then, chronic hepatitis E has been reported in several recipients of liver, kidney, heart and lung transplant who were on immunosuppressive therapy^[30,36-38]. The prevalence of post transplant infection by HEV in non endemic regions appears to be between 1%-2%^[39]. Based on available data, approximately 60% of solid organ transplant recipients exposed to HEV develop chronic infection, and within 2 years 10% progress to cirrhosis^[40].

Recurrence of chronic HEV infection has been reported after a second liver transplantation. A liver transplant recipient developed chronic hepatitis E and cirrhosis and a second liver transplant was performed after 7 years. HEV RNA continued to be detected from the serum and stool of the patient at the time of retransplantation and was also shown to be present in the retransplanted liver tissue^[36].

There has also been a case reported in which liver transplant from a donor with occult HEV infection induced chronic hepatitis and led to rapidly progressive cirrhosis and death of the recipient^[41].

Coexisting infection from more than one type of hepatotropic virus such as hepatitis C, hepatitis B and hepatitis E have been described. In patients with chronic HCV, acute hepatitis E infection has been shown to cause flare up of liver disease^[42]. Similarly acute hepatitis E infection in a well compensated cirrhotic can lead to decompensated liver disease or liver failure.

CHRONIC HEPATITIS E IN HEMATOLOGICAL MALIGNANCIES, HIV AND OTHERS

Chronic hepatitis E has also been reported in patients with hematological malignancies. Ollier *et al*^[43] reported a case of chronic hepatitis E in a 77 years old male with non-Hodgkin's lymphoma who was on rituximab. le Coutre *et al*^[44] reported a case of reactivation and long term persistence of HEV viremia fourteen weeks after allogeneic stem cell transplant (SCT) in a patient with Philadelphia chromosome positive acute lymphoblastic leukemia (ALL). The reactivation was attributed to immunosuppression or relapse of his ALL shortly after SCT. Since then several other series have reported prolonged HEV viremia and abnormal liver enzymes in patients receiving chemotherapy and stem cell transplantation^[45]. The first case of chronic HEV

in a patient with HIV was reported by Dalton *et al*^[46]. They described a 48 years old male with abnormal transaminases with a chronically low CD4 count (< 200) despite anti-retroviral treatment, who had persistent HEV RNA in serum for 18 mo and evidence of inflammation and cirrhosis on liver biopsy. Several cases have been reported since then^[47-49]. All cases of chronic hepatitis E in patients with HIV had CD4 count less than 200. Prevalence of chronic HEV in HIV patients is low and has been reported from 0% to 0.5% in different studies^[49-52].

Recently, few cases of chronic hepatitis E have also been reported in immunocompetent patients^[53-55].

TREATMENT OF CHRONIC HEPATITIS E

Kamar *et al*^[56] first demonstrated that reduction in immunosuppressive drugs that target T cells could help eradicate HEV in transplant recipients. Interestingly, all patients who cleared their virus after dose reduction of immunosuppressants had received a liver transplant, permitting greater reduction of immunosuppressive therapy (due to lower risk of acute rejection) as compared to kidney transplant patients. However, this effect was seen only in four out of sixteen patients in their study. The type of immunosuppressant therapy also affects chronic hepatitis E. Wang *et al*^[57] in a recent *in vitro* study showed that while steroids do not have any effect on HEV replication, calcineurin inhibitors stimulate and mycophenolic acid inhibits replication of HEV. They also demonstrated that the combination of ribavirin and mycophenolic acid had greater ability to inhibit HEV replication than ribavirin or mycophenolic acid alone.

As reduction in immunosuppression eradicated HEV only in about 30% of patients, Kamar *et al*^[58] used pegylated interferon α 2a at the dose of 135 mcg/wk for 12 wk in three liver transplant patients who developed chronic hepatitis E and failed to clear the virus in spite of decreasing the dose of immunosuppressive drugs. While all three patients had undetectable HEV RNA in serum and stool at 12 wk of treatment, one patient developed acute humoral graft rejection while HEV RNA was re-detected in another patient, 2 wk after completion of interferon therapy.

Due to the risk of graft rejection from decreasing dose of immunosuppressive drugs and using pegylated interferon α , Mallet *et al*^[59] studied the use of ribavirin in treating two patients with chronic hepatitis E (one was post kidney and pancreas transplant and other has idiopathic CD4 T lymphocytopenia). Both patients received ribavirin at a dose of 12 mg/kg per day for 12 wk. Liver enzymes normalized and HEV RNA was cleared from the serum and/or stool of both patients by week 4 of treatment and remained undetectable at 12 wk follow up. One patient needed dose reduction of ribavirin due to anemia.

Kamar *et al*^[60] performed a large retrospective multicenter case series to assess the efficacy of ribavirin on solid organ transplant recipients who had chronic

hepatitis E and HEV viremia. They included 59 patients in this study, of which 37 patients had received kidney transplants, 10 patients had liver transplantation, 5 patients had heart transplants, 5 patients had undergone combined kidney and pancreas transplantation and 2 patients were recipients of lung transplant. The median duration of therapy of ribavirin was 3 mo and the median dose was 600 mg daily. Fifty-four patients had genotyping performed and all cases were of the HEV genotype 3. They found that at the end of the therapy 95% of patients had clearance of HEV while 78% of patients had sustained virological response. Around 60% of patients had recurrence of HEV and 40% of these patients had sustained virological response following prolonged treatment course with ribavirin. This study demonstrated that a 3 mo course of ribavirin monotherapy is reasonable option to start with in chronic HEV infection to obtain sustained virological response. The main side effect of ribavirin was anemia, which was seen in 54% patients, with 12% needing blood transfusion.

Successful treatment of chronic hepatitis E in HIV positive patients with pegylated interferon (IFN)- α alone and combination of pegylated IFN- α and ribavirin has been reported^[48,61].

A recent systematic review evaluated the efficacy and safety of treatment with ribavirin in 105 patients and pegylated interferon in 8 patients with chronic hepatitis E^[62]. Sixty-four percent patients treated with ribavirin had undetectable HEV at 6 mo after cessation of treatment while only 2 out of 8 (25%) patients treated with pegylated interferon achieved sustained virological response. While the main side effect with ribavirin was anemia, needing erythropoietin in 35% patients and blood transfusion in 10% patients, pegylated interferon led to acute transplant rejection in 2 out of 8 patients. The authors concluded that ribavirin should be the antiviral medication of choice in chronic hepatitis E. However, the dose and duration of therapy needs to be evaluated further. Also, the combination of ribavirin and mycophenolic acid needs to be evaluated in clinical trials.

Based on available data, we recommend a decrease in immunosuppression (if feasible) as the first step in management of chronic hepatitis E. In the absence of an adequate response, we recommend ribavirin as the antiviral medication of choice in a dose of 600-800 mg per day for 3 mo with close monitoring for anemia.

PREVENTION METHODS

In endemic areas, the best method to prevent spread of HEV infection is by improving sanitation and maintaining good hygienic practices such as washing hands with soap. In non-endemic areas avoiding the intake of raw uncooked meat is the best way to avoid zoonotic transmission of HEV. The risk can be decreased but not eliminated by cooking the meat to temperatures greater than 70 °C, which has been shown to decrease the HEV

viral load^[63,64].

VACCINATION FOR HEPATITIS E

Two vaccines have been developed for the prevention of hepatitis E infection. Shrestha *et al.*^[65] in 2007 conducted a phase 2 randomized controlled trial of an HEV recombinant protein vaccine among 2000 healthy adults. This vaccine showed 95.5% efficacy after administration of 3 doses during a median follow up of around 2 years. However this vaccine never progressed beyond phase 2.

Zhu *et al.*^[66] published the results of a randomized, double blind phase 3 trial of a recombinant HEV vaccine among a much larger group of healthy adults. Three doses (30 mcg of purified recombinant hepatitis E antigen per dose) of the vaccine were given at 0, 1 and 6 mo and it showed 100% efficacy during the 12 mo follow up period after administration of the vaccine. No vaccination associated serious adverse effects were noted in the study. On extended follow up, up to 4.5 years, the vaccine was found to have efficacy of 86.8%^[67]. However, the ability of the vaccine to protect against different genotypes of the virus is as yet unclear, and data regarding its safety and efficacy in persons with chronic liver disease, and other vulnerable populations are needed prior to making recommendations for its widespread use.

CONCLUSION

Chronic hepatitis E has been mainly reported with genotype 3 but reports are emerging of other genotypes leading to chronic hepatitis. Therefore, careful testing, genotype categorization and recording of all chronic hepatitis E infections should be performed. Currently there is wide variation in the tests for diagnosis of HEV and there is a need for standardization of the assays. Effect of various immunosuppressant medications of replication of HEV needs to be studied *in vivo*. It is reasonable to start ribavirin treatment for chronic HEV to prevent the progression of liver disease and cirrhosis. However, more data are needed before recommendation for optimal treatment for hepatitis E can be made. There is need for increasing awareness amongst physicians of chronic hepatitis E infection as it is one of the treatable causes of chronic liver disease, especially in immunosuppressed individuals.

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