Chronic Hepatitis E Virus Infection and Treatment

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It is now well accepted that hepatitis E virus (HEV) infection can induce chronic hepatitis and cirrhosis in immunosuppressed patients. Chronic genotype-3 HEV infections were first reported in patients with a solid-organ transplant. Thereafter, cases of chronic HEV infection have been reported in patients with hematological disease and in those who are human immunodeficiency virus (HIV)-positive. HEV-associated extra-hepatic manifestations, including neurological symptoms, kidney injuries, and hematological disorders, have been also reported. In transplant patients, reducing the dosage of immunosuppressive drugs allows the virus to be cleared in some patients. In the remaining patients, as well as hematological patients and patients who are HIV-positive, antiviral therapies, such as pegylated interferon and ribavirin, have been found to be efficient in eradicating HEV infection. This review summarizes our current knowledge of chronic HEV infection, its treatment, and the extra-hepatic manifestations induced by HEV. (J Clin Exp Hepatol 2013;3:134–140)

It is now realized that HEV infection not only causes a self-limiting infection,[1] but can also evolve to chronic hepatitis in immunosuppressed patients, i.e., patients with a solid-organ transplant (SOT),[2] hematological patients,[3] and HIV-positive patients.[4] In addition, HEV-induced extra-hepatic manifestations have been reported.

Chronic HEV infection has been only described in patients infected by genotype-3. No case of chronic HEV genotype-1, 2, or 4 has been described. All cases have been autochthonous and have not been associated with travel.[1]

A diagnosis of chronic hepatitis used to be considered when persisting HEV replication lasted for at least 6 months. However, very recently, in the setting of organ transplantation, it has been observed that no spontaneous clearance of HEV occurs between 3 and 6 months after an acute phase: thus, this suggests that chronic HEV infection should be considered when HEV replication persists for more than 3 months after an acute phase.[5]

In this review, we will summarize the current knowledge on chronic HEV infection in immunosuppressed patients, its treatment, and will describe the extra-hepatic manifestations attributed to HEV.

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Abbreviations: HIV: human immunodeficiency virus; HEV: hepatitis E virus; SOT: solid-organ transplant; CSF: cerebrospinal fluid
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HEV INFECTION IN TRANSPLANT PATIENTS

Seroprevalence and Incidence of HEV Infection Among Adult Patients with a SOT

Serological tests have low and variable sensitivity,[6,7] and there are no commercially available nucleic-acid-based assays that detect HEV RNA in the serum and/or stools. Thus, because of considerable variability in the accuracy of in-house PCR tests,[8] caution needs to be applied when interpreting the following. HEV seroprevalence in adult patients with a SOT, assessed by different serological assays, ranges from 2.3 to 43.9%.[9–16] The prevalence of HEV infection, assessed by detecting HEV RNA, ranges from 0.9 to 3.5% (Table 1).[9,11–14,16,17]

Seroprevalence and Incidence of HEV Infection Among Pediatric Patients with a SOT

A few cases of acute and chronic HEV have been reported in liver- and kidney-transplant patients from Quebec, France, and Germany.[18–21] In these patients, HEV seroprevalence, assessed by different serological assays, ranged from 2.3 to 86%.[18,20]

Seroprevalence and Incidence of HEV Infection Among Patients with a Stem-cell Transplant

Only two studies have assessed the prevalence of HEV infection in adult patients with a stem-cell transplant: they found prevalence of 5.8% and 12.5%.[22,23] No patient had detectable HEV RNA, there were no cases of chronic hepatitis, and no HEV reactivation was observed in either study.[22,23] However, Tavitian et al[24] reported a case of persistent HEV infection in a patient who received vincristine/adriamycin/dexamethasone, after autologous stem-cell transplantation for a myeloma. In addition, a first case of

Table 1 Prevalence of hepatitis E virus infection defined by detection of HEV RNA.

Study	Country	Number	Transplanted organs	Prevalence
Legrand-Abravanel et al[9]	France	700	KT, LT, SPK	3.2%
Legrand-Abravanel[10]	France	171	KT, LT	3.5%
Moal et al[16]	France	1350	KT	1.2%
Pischke et al[11]	Germany	226	LT	0.9%
Pischke et al[12]	Germany	274	HT	1.5%
Haagsma et al[13]	The Netherlands	285	LT	1.75%
Pas et al[14]	The Netherlands	1200	SOT	1%
Riezebos-Brilman et al[17]	The Netherlands	468	Lung transplantation	2.1%

Abbreviations: KT, kidney-transplant; LT, liver transplant; SPK, simultaneous pancreas–kidney-transplant; HT, heart transplant; SOT, solid-organ transplant.

HEV-related cirrhosis in a child who had undergone a bone-marrow transplant was reported.[25] A single case of HEV reactivation has been also reported in a patient with acute lymphoblastic leukemia after an allogeneic stem-cell transplant.[26]

Mode of HEV Transmission Among Patients with a SOT

In immunosuppressed patients, HEV is transmitted via the same modes as in the general population, i.e., fecal and/or an oral route for HEV genotypes 1 and 2, and by the consumption of animal products, such as undercooked pork, offal, sausages, and mussels, for genotypes 3 and 4.[1] In organ transplant patients, eating pork products, mussels, and game meat have been associated with HEV infection.[27] Thus, patients with an organ transplant are advised not to eat undercooked meat: HEV is only inactivated by temperatures >70 °C.[28]

In addition to the classical routes, HEV can be transmitted by blood transfusion, via the allograft, or by nosocomial transmission. Although, no case of HEV transmission via blood transfusion has been reported in the transplant population,[9] HEV seroprevalence in blood donors is high[29] and cases of HEV transmission via blood products have been reported in other populations.[30–32] Hence, if HEV infection is detected a few days after a blood transfusion, this mode of contamination should be investigated.

To date, only one case of occult HEV transmission via a liver allograft has been reported in the literature.[33] HEV RNA was detected in a liver biopsy obtained from the donor before transplantation, but not in his serum. Phylogenetic analyses showed that the donor's and recipient's HEV strains were identical.[33] Despite a high seroprevalence of HEV among organ donors in a highly endemic area, we have not identified any HEV transmission via the transplanted organ.[9] Even though it would be of interest, to date, there are not sufficient data to recommend screening all blood and organ donors for HEV.

HEV transmission has been reported in a hemodialysis unit[34] and a hematology ward.[35] Hence, we wondered whether nosocomial HEV transmission could occur in organ transplant recipients who have frequent hospitalizations, especially within the early post-transplant period. Thus, we isolate HEV RNA-positive transplant patients admitted to hospital to avoid possible transmission to other transplant patients.

Natural History of HEV Infection in Patients with a SOT

After the first reported cases of chronic HEV infection in 2008,[2] the prevalence of chronic HEV in patients with a SOT in Europe and the US has dramatically increased.[11,12,14,18,36–48]

A large multicenter retrospective study, which included 85 adult patients with a SOT (kidney-, liver-, kidney–pancreas-, islet-, heart-, and lung-transplants) showed that 34.1% had spontaneous clearance of HEV within the first 6 months after HEV was diagnosed and no HEV reactivation later on, whereas 65.9% developed chronic hepatitis.[49] Interestingly, in contrast to non-immunosuppressed patients who usually present to hospital with jaundice,[50] when HEV was diagnosed, only 32% of patients were symptomatic.[49] Fatigue was the main reported symptom, and only one patient was icteric. Liver-enzyme levels were increased (~300 IU/L), but were much lower than those usually observed in immunocompetent patients (~3000–5000 IU/L). HEV seroconversion may be delayed and or may not occur.

Strikingly, in the above study, 9 out of the 85 patients (9.4%) developed cirrhosis.[49] Several other cases of HEV-induced cirrhosis have been reported.[12,18,33,36–38,40,49] In one study, liver fibrosis rapidly evolved in transplant patients who were chronically infected by HEV, and this led to decompensated cirrhosis and death.[40] Slow HEV quasispecies diversification during the first year after infection has been associated with rapidly developing liver fibrosis.[51]

Risk Factors for Chronic HEV Infection in Patients with a SOT

Few studies have assessed the risk factors for chronic HEV infection in transplant patients. Clinical and immunological data suggest that persistent HEV infection occurs in patients who are deeply immunosuppressed. Indeed, CD2, CD3, and CD4 T-cell subsets are significantly lower, and evolve in a shorter time after transplantation in

patients with chronic hepatitis compared to those with resolved hepatitis.[2,49] The use of tacrolimus, a more potent immunosuppressant than cyclosporine A, has been also associated with chronic HEV infection.[49] In addition, HEV-specific T-cell proliferative responses were decreased in transplant patients, particularly in those with chronic hepatitis.[52,53] Patients who developed chronic infection also have lower serum concentrations of the IL-1 receptor antagonist and the IL-2 receptor during acute phases of HEV infection compared to patients with resolving hepatitis.[51] Increased serum concentrations of the chemokines implicated in leukocyte recruitment to the liver, such as RANTES, MIP-1β, MCP-1, and CXCL8, have been associated with persistent infection.[51]

In a large multicenter study, the use of tacrolimus (compared to cyclosporine A) and a low platelet count were the only two independent predictive factors for chronic hepatitis E in patients with a SOT.[49] Pischke et al[12] found that the use of mycophenolate mofetil was associated with HEV clearance in heart transplant patients, although this data needs to be confirmed. In addition, with acute phase HEV infection, a large heterogeneity of quasispecies has been observed in patients with persistent HEV compared to patients with resolving hepatitis.[51]

Treatment of HEV Infection in Infected SOTs

Large studies have not yet established a therapy for HEV infection, although reducing the dose of immunosuppressants can achieve HEV clearance in nearly a third of patients.[40,49] A few liver-transplant patients with chronic HEV infection were given a 3-month (n = 3) or a 12-month (n = 1) course of pegylated interferon (135 μg/week): a sustained virological response was observed in three of the four patients.[54,55] *In vitro*, it has been shown that HEV downregulates IFN-α-induced gene expression.[56]

Several small series have also evaluated ribavirin as a monotherapy to treat chronic HEV infection in adult patients with a SOT[12,17,41,43,45,46,57,58]; 3–6-month courses of ribavirin therapy were given. A sustained virological response was observed in the majority of patients. Very recently, ribavirin therapy was also successfully used in a pediatric transplant patient.[21] Larger studies are required to determine the optimal dose and duration of ribavirin in this setting.

Treatment of Patients who are Candidates for Organ Transplantation or Re-transplantation

Candidates for organ transplantation who are infected by HEV have to be treated before transplantation. Indeed, HEV infection may recur after re-transplantation, leading to recurrence of chronic hepatitis in patients who were not cleared of the virus previously.[38] Hence, in cases of fulminant hepatitis that require transplantation, HEV infection has to be ruled out and HEV clearance should be achieved before transplantation or re-transplantation. In the setting of "acute- on- chronic hepatitis" with severe fulminant hepatitis, a short course of ribavirin can obtain complete recovery and, thus, avoid the need for liver transplantation.[59]

A hemodialysis patient with chronic HEV infection was successfully treated with a 3-month course of pegylated interferon alpha 2a (135 μg/week). Interestingly, kidney-transplant patients infected with HEV, who are then cleared of the virus and maintain sustained clearance, i.e., HEV clearance for at least 6 months, do not relapse after re-transplantation despite receiving an immunosuppressive regimen that includes an induction therapy.[60] Hence, dialysis patients previously infected by HEV can be proposed for re-transplantation.

HEV INFECTION IN HIV PATIENTS

Shortly after the first report of chronic HEV infection in recipients of a SOT, chronic HEV infection with associated cirrhosis was described in an individual infected with HIV-1.[4] Subsequent analysis showed that the HEV genotype-3 strain recovered from this patient's stool contained an insertion of 58 amino acids from a human ribosomal protein gene,[61] confirming that a human/hepatitis E recombinant virus exists. However, HEV co-infection in patients with HIV is not common and, to date, less than 20 cases have been documented in the literature, and only a handful have had chronic infection, the majority of these cases become cleared of HEV spontaneously.[4,62–72] In contrast to recipients of a SOT, the key risk factor that determines the development of chronic infection in HIV patients is a low CD4 count. In the five chronic cases described so far, all had CD4 counts <250 mm^3. As in transplant recipients, patients with chronic HEV had no symptoms attributable to HEV, the only clue to diagnosis was low-grade fluctuating transaminitis with alanine aminotransferase within the 100–300 IU/L range.

The incidence of HEV infection, defined by detecting HEV RNA in the serum, is very low, ranging from 0 to 1.3%.[62–66,73–77] One study retrospectively tested for HEV in 194 HIV-positive US military beneficiaries and showed that HEV was the cause of abnormal liver function tests in only 4% of HIV-infected individuals.[65] Serum transaminitis caused by HEV was no more common in this population than in the general population.

The route of HEV acquisition in HIV-infected patients is uncertain. A small case–control study suggests that sexual transmission is unlikely.[76] Early research postulated intravenous drug use as an independent risk factor for locally acquired HEV infection.[78] However, a retrospective study of HEV seroprevalence among HIV/hepatitis C co-infected patients in France found anti-HEV IgG antibodies in 5.3% (2/38) of patients, which was considerably lower than the seroprevalence in healthy blood donors and was not influenced by intravenous drug use.[79]

There are few data regarding treatment of HEV in HIV patients: of the three patients treated, all achieved viral clearance. One patient in the UK was treated with pegylated interferon as a monotherapy for 6 months, but was not cleared of HEV until he received a further 3-month combined therapy of ribavirin plus pegylated interferon.[80] A second patient from the UK was successfully treated with pegylated interferon as a monotherapy.[81] The third case is perhaps the most interesting. The patient was from South Africa, and like the European cases, the HEV was also genotype-3. The patient had a very low CD4 count, and cleared HEV following the introduction of anti-retroviral therapy, associated with an immune reconstitution hepatitis.[82] As in transplant recipients, chronic HEV infection in patients with HIV has only shown to be due to HEV genotype-3. How HIV and HEV interact in Africa and Asia, where HIV and HEV genotypes 1 and 2 are endemic, is not known, and merits further study.

CHRONIC HEV INFECTION IN PATIENTS WITH A HEMATOLOGICAL MALIGNANCY

Chronic HEV infection has been reported in hematological patients receiving chemotherapy.[3,24,30,41,83,84] The clinical and laboratory features of chronic HEV in these patients are similar to those in recipients of a SOT. A few cases have been treated successfully with pegylated interferon or ribavirin as monotherapies.[41,84,85]

HEV-INDUCED EXTRA-HEPATIC MANIFESTATIONS

Several extra-hepatic manifestation related to HEV have been reported including neurological, renal, pancreatic and hematological manifestations.

Neurological Manifestations

During the acute phases of HEV genotype-1 and -3 infections, neurological manifestations, such as Guillain–Barré syndrome,[48,86–93] Bell's palsy,[94] neuralgic amyotrophy,[95,96] acute transverse myelitis,[97] and acute meningoencephalitis[90,98] have been reported. Neurological symptoms occur in an estimated 5.5% of HEV patients.[99] Interestingly, HEV RNA has been detected in the cerebrospinal fluid (CSF) of four patients with chronic HEV infection.[99] Clonal HEV sequences in the serum and CSF of a kidney-transplant patient with chronic hepatitis and neurological symptoms showed quasispecies compartmentalization, which suggests that neurological symptoms could be linked to the emergence of neurotropic variants.[100] In addition, cases of anti-ganglioside GM1-positive and anti-GM2-positive Guillain–Barré syndrome, caused by HEV infection, have been reported.[91,92] Very recently, a case of Guillain–Barré syndrome has been reported associated with severe necrotizing myositis, which occurred in a liver-transplant patient during an acute HEV-3 infection phase, but who recovered after ribavirin therapy.[101] Further studies are needed to evaluate the role of HEV in Guillain–Barré syndrome when it has no known etiology.

Kidney Manifestations

Impaired kidney function after kidney- and liver transplantation in patients with HEV infection has been observed.[102,103] In addition, glomerular lesions, such as membrano-proliferative glomerulonephritis and membranous glomerulonephritis, have been reported in kidney- and liver-transplant patients.[104] Furthermore, cryoglobulinemia has been detected in transplant patients with chronic HEV-3 infection. Further studies are required to confirm these preliminary data.

Other HEV-related Extra-hepatic Manifestations

Only HEV genotype-1-induced acute pancreatitis has been reported[104–107]: no cases of genotype-3-induced pancreatitis have been reported. In addition, a few cases of severe thrombocytopenia have been observed during the acute phase of HEV infection.[108,109] Very recently, a case of HEV-associated aplastic anemia was reported.[110]

CONCLUSIONS

In immunosuppressed patients, particularly those with a SOT, HEV can evolve to chronic hepatitis and cirrhosis. In addition, HEV can cause extra-hepatic manifestations, such as neurological disorders and kidney injury. In the absence of a robust serological test, diagnoses should be based on detecting HEV RNA in the serum and/or stools. In the absence of spontaneous clearance of HEV, the use of an anti-viral therapy, mainly ribavirin as a monotherapy, and lowering immunosuppression dose (in transplant patients), may allow HEV clearance in the majority of patients.

CONFLICTS OF INTEREST

All authors have none to declare.

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