Journal of Clinical Virology 80 (2016) 102–106

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Review

Hepatitis E virus infection in the HIV-positive patient

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ARTICLE INFO

Article history:
Received 29 March 2016
Accepted 16 May 2016

Keywords:
Hepatitis E virus
HIV
CD4 counts
Risk factors

ABSTRACT

Hepatitis E virus (HEV) is a RNA virus that can cause hepatitis. In immunocompetent individuals, infection with HEV usually leads to asymptomatic seroconversion. However, in immunosuppressed patients, such as transplant recipients, HEV can develop into a chronic infection. Studies regarding the seroprevalence and clinical implications of HEV in patients infected with the human immunodeficiency virus (HIV) are conflicting. Levels of CD4 count in blood seem to be the most widely associated risk factor, while other factors such as meat consumption or proximity to animals are less clearly associated with HEV infection. Progression to chronicity, as well as extrahepatic manifestations of HEV seem rare in HIV, and the implications of HEV in liver disease progression are poorly understood in the HIV-infected. In this review we describe the epidemiology, risk factors, and clinical implications of HEV infection in individuals infected with HIV.

Contents

1. Introduction

Hepatitis E virus (HEV) is a single-stranded, non-enveloped, RNA virus, which is transmitted through enteric route and can cause hepatitis. HEV is considered endemic in many developing countries from Asia and Africa, where major outbreaks occur due to the consumption of contaminated food or water, generally associated to HEV genotypes 1 and 2 [1,2]. These HEV variants only infect primates, and are usually self-limited, but can cause fulminant hepatitis in pregnant women and potentially in patients with pre-existing liver disease [3,4]. In developed and non-endemic countries, sporadic cases of HEV occur in patients with no travel history, due to HEV genotypes 3 and 4. Many of these infections have been linked to ingestion of raw or undercooked meat of wild boar, pig and deer, or to direct contact with these animals, which can be infected by these HEV variants, supporting the concept that transmission of these genotypes is zoonotic [5–7]. Interestingly, a recent report first described a zoonotic transmission of HEV genotype 7 from a camel to a human, in a solid organ transplant recipient, indicating that human infections with other genotypes could occur in the future [8].

When cases occur in immunocompetent individuals, infection with HEV usually leads to silent seroconversion and a chronic course is unlikely [9]. However, in recent years it has been found that individuals who are immunosuppressed, particularly solid

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http://dx.doi.org/10.1016/j.jcv.2016.05.006
1386-6532/

organ transplant recipients and bone marrow transplant recipients can develop chronic infection with HEV, as well as acute infection or reactivation of the virus [10–13]. In individuals with immunosuppression from HIV infection the epidemiology, risk factors, and long-term complications are less well understood and more complex than initially estimated. Many questions remain unexplained, particularly in regards to route of infection (zoonosis-related, fecal-oral, transfusion), factors that affect prevalence (CD4 count, geographic area, customary habits) and if the infection affects the long term condition and function of infected livers. In this review we describe the variable epidemiology of HEV and HIV co-infection, the risk factors for HEV in HIV-infected individuals and the clinical implications of the co-infection.

2. Epidemiology of HIV and HEV

The seroprevalence of HEV in the HIV-infected population has not been well established. Several studies have evaluated the presence of immunoglobulin G (IgG) anti-HEV, immunoglobulin M (IgM) anti-HEV and/or HEV RNA in serum of HIV+ patients, with a variety of reported prevalence rates that depends on the geographic area and target population [14–16]. Table 1 summarizes the available information of HEV prevalence studies performed in HIV infected populations. When considering HEV IgG seroprevalence, there is a wide range of rates, varying between 1% and 45% [17–20]. This is likely related to the local circulation of HEV and/or to risk factors associated to HEV infection, as well as the sensitivity and specificity of different tests. In European countries the reported seroprevalences does not exceed 26%, with some countries like Spain and Italy, showing dissimilar values even within the same country [15,16,21–27]. In the Americas, prevalence rates are similar to Europe, with the highest percentage being that of the USA at 19.5% [28]. Interestingly, the highest prevalence rates (between 30% and 45.3%) were reported in studies from Africa and Asia, probably reflecting the endemicity for HEV of these areas [19,20,29]. Although no direct comparison is available, most studies show increase seroprevalence of HEV in those infected with HIV, when comparing to those HIV-negative, although there is much variability in this area (Table 1).

Regarding HEV IgM detection, many studies report positive results that indicate recent or acute infections, but this does not always correlate with the presence of HEV RNA in blood (Table 1). Studies that performed HEV RNA detection through PCR showed a lower frequency of positive results than those assessing IgG. Interestingly, one would expect higher frequency of HEV RNA positive results in those IgM positive or in the absence of seropositivity. In this regard, it is important to mention that the value of HEV RNA detection in the HIV+ population with marked immunosuppression is controversial, since several studies observed positive results for PCR in absence of specific IgG and/or IgM tests [29,30]. The reason for this deficiency of antibodies could be that HIV patients may lack, or have a delayed, antibody production against several viral co-infections [15,31].

Available HEV seroprevalence studies in HIV-infected individuals, however, have several limitations: (a) some of the studies tested small populations; (b) many were carried out using different commercial kits, which can yield different results in the same population; (c) some prevalence rates are based on confirmation results by western blot or immunoblot instead of only by Elisa assays [14,15]. All these discrepancies make comparisons across the globe very difficult to assess. Nonetheless, based on the available reports, there seem to be an increased overall seroprevalence of HEV IgG in HIV-infected individuals when compared to non-infected persons, although this varies according to the geographical region, with data on HEV IgM and RNA to scarce to draw reasonable conclusions.

2.1. Risk factors for HEV among HIV-infected patients

As mentioned above, studies assessing which HIV-infected individuals are at higher risk of HEV infection are scarce and the results are discordant.

Several variables that could be associated to HEV infection in HIV infected individuals have been proposed, this include: gender, age, ethnicity, intravenous drug use, sexual orientation, contact with pigs (farming), pork consumption, CD4 count in blood, HIV viral load, use of ART, AIDS stage, co-infection with HAV, HBV, HCV and cirrhosis (Table 1). However, the strength of the evidence varies significantly among different risk factors. Despite pork consumption being widely reported as a risk factor for HEV among immunocompetent population, only one study found a statistical association between HEV infection and the consumption of undercooked pork in HIV+ individuals [32–36]. Interestingly, this study found no association between sexual orientation or CD4 counts and HEV infection but found a trend to higher prevalence in non-white individuals [32].

High HEV seroprevalence was observed among HIV-infected patients with cirrhosis. This observation is in agreement with data reported in non-HIV infected patients, and suggests that individuals with cirrhosis are at a high risk of acquiring HEV infection [22]. Although a reverse causality could be argued as we discuss below. One possible explanation for these findings could be the immune dysfunction observed in patients with cirrhosis, in addition to that of HIV. These patients can develop a decreased innate immune response with a reduced surveillance function of the liver through damage of the reticulo-endothelial system and impaired synthesis of innate immunity proteins and pattern recognition receptors [37,38]. In addition, circulating NK cells, which are particularly important for viral response, are also defective in cirrhosis and show a poor response to cytokine stimulation [39].

One common factor associated with HEV infection both in immunocompetent individuals and those immunosuppressed from HIV is increasing age [25,28,40–43]. Although no particular age cutoff seem to define an augmented risk for HEV, the high rates observed in elderly groups could be explained by cumulative exposure over time.

Several studies comparing data in countries with high prevalence for HEV show that the greatest regional differences are usually seen among children, suggesting that HEV spreads earlier in life among the population of Asia and Egypt than of the rest of the world. Independently of the overall prevalence, anti-HEV is acquired earliest in life in endemic regions for HEV genotype 1 in comparison with the regions endemic for HEV genotype 3 [44].

Severe immunosuppression, defined by a decrease in CD4 cells to <100–200 cells/mm^3, has been the factor most widely associated with HEV infection in HIV+ individuals [15,19,30,45,46]. According to a literature search, 8 documented cases of positive HEV real-time PCR amplification in HIV-positive individuals have been reported [30,45,47–51]. Of these, 5 cases had CD4 counts >200 cells/mm^3 and sought treatment due symptoms of acute infection with post-treatment viral clearance. In the other 3 reported cases, all of whom had CD4 counts <200 cells/mm^3, persistent hepatitis developed. Nonetheless, a recent study reported the case of a woman who acquired HEV infection with low CD4 count (<200 cells/mm^3) but remained persistently HEV viremic even as CD4 count increased above 200 cells/mm^3 post-infection [52].

Based on the reviewed studies above, HIV alone does not seem to be a risk factor for HEV infection. However, once the virus affects the immune system to a significant degree, as measured by CD4 counts, individuals become at risk for HEV infection. In summary, the data suggests that patients infected with HIV with low account of CD4 cells can be considered a risk group for HEV infection.

Table 1
Published studies on HEV and HIV coinfection.[10]

Country	IgG HEV% (positive/tested)	IgM HEV% (positive/tested)	Risk factor analyzed	Risk factors with statistical association ($p < 0.05$)	Chronicity	References
Spain	4.4% (8/184)	1.6% (3/184)[6]	CD4 account, age, gender, HBV-HCV coinfection, cirrhosis, parenteral/sexual transmission risk	NS	POS	Kaba et al. [59]
Spain	9% (22/238)	0%[5]	CD4 account, HIV viral load, HBV-HCV coinfection, IVDU, cirrhosis, age, gender, ALT/AST, ART	Cirrhosis	POS	Jardid et al. [23]
Spain	9.2% (22/238)	ND	CD4 counts, ART	CD4 counts[9]	NEG	Riveiro Barciela et al. [42]
Spain	10.4% (45/448)	7% (3/45)[2]	CD4, Gender	NS	NEG	Mateos-Lindemann et al. [60]
Spain	21% (189/894)	ND[2]	CD4 counts, HIV viral load, HBV- HCV coinfection, age, gender, ALT/AST, ART	Age	NEG	Rivero Juarez et al. [35]
Spain	26% (161/613)	ND[2]	CD4 account, age, gender	CD4 counts, Gender (M > F), Age	NEG	Pineda et al. [15]
Italy	19.4% (14/72)	0	HIV infection	HIV infection	NEG	Rapicetta et al. [38]
Italy	2% (2/100)	50% (1/2)[2]	HIV infection, AST/ALT	NS	NEG	Scotto et al. [61]
Italy	6.7% (34/509)	14.7% (5/34)	NR	NS	NEG	Scotto et al. [57]
Greece	7.3% (18/243)	0	HIV time of infection, HAV- HBV- HCV coinfection, Sexual orientation, ART	Age	NR	Politou et al. [34]
France	9% (22/245)	2.25% (5/245)[4]	CD4 counts, CD8 counts, HIV viral load, HIV clinical status, Liver function, age, gender, ethnicity, ALT/AST, parenteral/sexual transmission risk.	CD4	NEG	Renou et al. [40]
France	3.7% (4/108)[1]	0.9% (1/108)[2,8]	CD4 account, HIV viral load, HBV- HCV coinfection, ALT/AST, ART	NS	NEG	Sellier et al. [62]
France	1.5% (4/261)	0%	CD4 account, age, HBV- HCV coinfection, ALT/AST	NS	NEG	Maylin et al. [63]
Scotland	1.04% (1/94)	100 (1/1)	NR	NS	NR	Bradley Stewart et al. [64]
England	9.4% (13/184)	0%	CD4 counts, HIV viral load, sexual transmission route, pork contact, pork consumption	pork consumption	NEG	Keane et al. [28]
Switzerland	2.6% (19/735)[1]	ND[7]	CD4 counts, HIV viral load, age, HBV-HCV, sexual orientation, IVDU, transfusion, prison history, cancer, BMI, Alcohol consumption, ALT value, Duration of ALT elevation, ART	CD4 account (CD4 $\leq$ 350 cell/mm3), Duration of ALT elevation, Gender (F > M), Asian origin.	POS	Kenfak Foguena et al. [20]
Holland	11.7% (30/256)	0%	CD4 account, HBV- HCV coinfection	NS	NR	Hassing et al. [65]
Croatia	1.1% (1/88)	12.5% (11/88)[3]	NR	NS	NR	Dakovic Rode et al. [66]
Gabón	7.1% (13/183)	0%	HIV Viral load	HIV Viral load	NEG	Caron et al. [67]
Ghana	45.3% (182/402)	0.7% (1/182)	CD4 counts, AST/ALT	CD4 counts	NEG	Feldt et al. [17]
Cameroon	14.2% (42/289)	ND	CD4 counts, ALT/AST	CD4 counts	NEG	Feldt et al. [17]
Nigeria	30% (24/80)	4.2% (1/24)	NR	NS	NR	Junaid et al. [18]
Cambodia	30% (247/825)	1.1 (9/825)	Fever, age, gender, ALT/AST	NS	NEG	Nouhin et al. [19]
Malaysia	10.3% (15/145)	4.1% (6/145)	Age, IVDU, Sexual Orientation, transfusion, endemicity	Age	NR	Ng et al. [36]
Australia	6.3% (12/191)	ND[3]	ALT/AST	NS	NEG	Yong et al. [58]
USA	19% (32/166)	0.9% (2/133)	CD4 counts, HIV viral load, age, HCV coinfection, ethnicity, ALT/AST	Age, HCV coinfection	NR	Sherman et al. [16]
USA	4% (7/194)	3% (5/194)	CD4 counts, HIV viral load, age, gender, ethnicity, HBV-HCV coinfection, ALT/AST, ART	HIV Viral load, CD4 counts[9]	NEG	Crum-Cianflone et al. [41]
Argentina	6.6% (32/484)	ND	IVDU, AIDS, gender	NS	NR	Fainboinm et al. [67]

HEV, hepatitis E virus; MSM, men who have sex with men; IDU, intravenous drug use; BMI, body mass index; ALT, alanine aminotransferase; ART, antiretroviral therapy; NS, Non-significant (NS), $p > 0.05$.

[1] Patients with unexplained alanine aminotransferase elevation.
[2] HEV RNA (+) in one patient.
[3] HEV RNA (+) in five patients.
[4] HEV RNA (+) in two patients.
[5] HEV RNA (+) in three patients.
[6] Patients with CD4 value $\leq$50 cell/μl. HEV genotype 3c.
[7] Patient with IgG anti −HEV (−), HEV RNA (+) genotype 3c, CD4 depletion and ART.
[8] HEV genotype 3e.
[9] Trend to association with HEV infection but not statistically supported.
[10] References update until September, 2015.

2.2. Clinical implications of HEV in the HIV-infected patient

In immunocompetent hosts the clinical features of HEV infection have a wide variety of symptoms, ranging from completely asymptomatic or acute hepatitis, to liver failure [7]. The later event is found more frequently in cases of infection during pregnancy [53]. In cases where symptoms are present, jaun-

dice, fatigue, fever, joint pain and sometimes abdominal pain are observed. Some patients might present with loss of appetite, loss of weight and a purpuric rash [54]. In general, clinical manifestations represent a myriad of signs and symptoms typical of any viral acute hepatitis, and when present, usually resolve within 3–6 weeks [54]. When HEV infection becomes chronic in the immunosuppressed host, it is usually asymptomatic, although some individuals might complain of abdominal pain, jaundice and fatigue. Extra-hepatic manifestations have been associated with HEV and they include Guillain-Barre syndrome, bilateral brachial neuritis, peripheral neuropathy, encephalitis, thrombocytopenia and pancreatitis, among others [55–58]. Most of these presentations are associated to HEV in solid-organ or bone marrow transplant recipients. In those infected with HIV the clinical expression of acute HEV is far less common, likely due reduced cytokine response and decreased antigen presenting capability from the organism [59]. Extrahepatic manifestations of HEV in the setting of HIV have randomly been reported. A case of peripheral neuropathy as extrahepatic manifestation of HEV in an HIV-infected individual was described in 2009 [60]. This patient improved following treatment of HEV with pegylated α-interferon and ribavirin. Overall, although the prevalence of HEV IgG in HIV is higher than that in immunocompetent controls within the same geopopulation, the extrahepatic manifestations or progression to chronicity in HIV have not been reported with the same frequency as in other forms of immunodeficiency. Large studies from Italy, Australia, Ghana and Cameroon, found increased seroprevalence of HEV in HIV-infected individuals but persistent detection on HEV RNA in these samples, which would suggest chronicity, was minimal to none [19]. The first case of chronic HEV in a patient with HIV was reported by Dalton et al. This group described a 48 years old male with abnormal transaminases with a chronically low CD4 count (<200 cells/mm3), despite antiretroviral treatment, who had persistent HEV RNA in serum for 18 months and evidence of inflammation and cirrhosis on liver biopsy [60].

Most descriptions of chronic or clinically evident HEV in HIV are based on individual case reports or small case series. A recent study in almost 3000 plasma samples from HIV-infected persons in the United States showed only one case compatible with chronic HEV infection [52]. These findings generate the question of whether HEV infection can play a role in the progression of advanced fibrosis or cirrhosis in HIV-infected patients. In this regards, a lack of chronicity and therefore lack of continuous immune response creating a prolonged inflammatory environment in the liver would not make a case for HEV increasing the risk of liver fibrosis in HIV-infected patients (beyond the effects of the HIV virus alone, that is). Several reports, however, have shown some association with cirrhosis and HEV infection during HIV infection. Jaqjit et al. described a single patient in which a case of cryptogenic cirrhosis was probably attributed to HEV infection [62]. Two studies from Spain found an increased prevalence of cirrhosis in individuals infected with HEV and HIV compared to those with HIV who were seronegative for HEV. It should be taken into account that these are prevalence-only studies, and in one of them [22] 99% of patients were co-infected with either hepatitis B virus or hepatitis C virus [22,23]. Further studies are needed to address whether infection or exposure to HEV plays a role in the development of liver fibrosis in HIV-infected individuals. When the infection with HEV occurs following that of HIV (in the setting of an immunosuppressed organism), it could be argued that the effect of HIV on T cells and Kupffer cells could hamper the immune-mediated response during HEV infection, with production of low-level inflammatory cytokines that lead to fibrosis. However, there is a paucity of understanding in this area of research. Moreover to our knowledge, no study has evaluated if HIV control through antiretroviral therapy could affect the interplay between both viruses and liver pathophysiology.

3. Conclusions

HEV is generally under diagnosed in clinical settings. Although several studies showed a risk for chronicity of HEV in the immunosuppressed patient due to solid organ or bone marrow transplant, little is known about the effect of HEV during HIV infection. Most studies to date seem to show an increased seroprevalence of HEV in HIV infected individuals, particularly in those with low CD4 counts, with little evidence of predisposition to chronic HEV in this population. Nonetheless, some reports are concerning for an increased prevalence of cirrhosis in the HIV/HEV co-infected and further research in this area is needed.

Conflict of interest

No conflict of interest by any of the authors.

Competing interests

None declared.

Ethical approval

Not required.

Acknowledgment

Partially funded by American College of Gastroenterology, Clinical Research Award to JD.

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