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Original article

High prevalence of antibodies against hepatitis E virus in HIV-infected patients with unexplained liver disease

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ABSTRACT

Objective: To look for evidence of hepatitis E virus (HEV) exposure in HIV-infected patients with unexplained elevations of liver stiffness (LS).
Methods: Case–control study conducted in 31 HIV-infected patients with unexplained elevations of LS and in 31 HIV-controls with normal LS, matched by age, sex and CD4 cell-counts. Serum HEV antibodies were tested by two ELISA procedures and by Immunoblot. We defined exposure to HEV as the detection of serum HEV antibodies by at least one of the two ELISA assays, provided that it was confirmed by Immunoblot. A real-time PCR RNA assay was conducted in all plasma samples to identify subjects with active HEV infection.
Results: Exposure to HEV was demonstrated, according to the criteria used in this study, in 9 (29%) of the cases, whereas it was shown in 5 (16%) of the controls ($p = .3$). Serum HEV RNA was detected in none of the controls and in only in one case. This patient had a documented chronic hepatitis E with progression to cirrhosis.
Conclusions: HEV antibodies are frequently found in HIV-infected patients with unexplained liver disease.

Prevalencia elevada de anticuerpos frente al virus de la hepatitis E en pacientes infectados por el VIH con enfermedad hepática de origen incierto

Palabras clave:
Virus de la hepatitis E
VIH
Fibrosis hepática
Cirrosis
Rigidez hepática

RESUMEN

Objetivo: Evaluar la existencia de exposición previa al virus de la hepatitis E (VHE) en pacientes infectados por el VIH con elevaciones inexplicadas de rigidez hepatica (RH).
Métodos: Estudio caso-control realizado en 31 pacientes con infección por el VIH y elevaciones inexplicadas de RH y 31 controles infectados por el VIH con RH normal, apareados por edad, sexo y recuento de células CD4. Se investigó la presencia de anticuerpos en suero frente al VHE mediante dos técnicas de ELISA y por Inmunoblot. La exposición previa al VHE se definió como la detección de anticuerpos séricos mediante al menos una de las dos técnicas de ELISA que se confirmó posteriormente mediante Inmunoblot. En todos los pacientes se realizó una PCR en tiempo real para identificar a aquellos pacientes con infección activa por el VHE.
Resultados: Se demostró la presencia de exposición previa al VHE, de acuerdo a los criterios usados en el estudio, en 9 (29%) de los casos y en 5 (16%) de los controles (p = 0.3). La PCR en tiempo real confirmó la presencia de RNA del VHE en el suero de uno de los casos y en ninguno de los controles. Este paciente presentó una hepatitis crónica por VHE documentada con progresión a cirrosis.

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Conclusiones: Los pacientes infectados por VIH con enfermedad hepática de origen inexplicado presentan una frecuencia elevada de anticuerpos frente al VHE.

Introduction

Autochthonous hepatitis E virus (HEV) is an emerging infection in HIV patients in developed countries.[1–4] Epidemiological data from Spain have suggested that HIV may be an independent risk factor for autochthonous HEV.[5,6] In a retrospective study, HEV infection accounted for 4% acute liver abnormalities in HIV-infected individuals.[7] Besides HEV-related unexplained acute elevations of liver enzymes, chronic HEV infection with rapid progression to cirrhosis has been reported in HIV-infected patients.[8–10]

Unexplained elevations of liver stiffness (LS) were found in 11% of the HIV-infected patients without hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infection from our cohort.[11] Liver histology proved several sort of liver damage virtually in all patients with unexplained elevations of LS.[11] In those with normal values of LS, sequential examinations revealed that 7% of them developed persistent elevations of LS, which were mainly attributed to fatty liver disease.[12] However, previous HEV infection was not routinely investigated in these patients. In fact, it has been hypothesized that subclinical hepatic steatosis or fibrosis could be a host risk factor for clinical disease expression in patients exposed to HEV.[13]

Our objective was to look for evidence of HEV exposure in HIV-infected patients with unexplained elevations of LS.

Methods

Study design and patients

This was a case-control study conducted in two hospitals from Southern Spain. We selected as cases all patients fulfilling criteria of abnormal LS of uncertain origin as previously described among those who attended both institutions.[11,12] Briefly, we selected HIV-infected patients with a LS ≥ 7.2 kiloPascals (kPa) in two consecutive visits, without previous exposure to HBV or HCV as determined by a negative hepatitis B surface antigen, negative HCV antibodies and a negative serum DNA HBV and RNA HCV PCR assessment, and without evidence of other causes of liver disease. Forty-four patients fulfilled these criteria before 30th June 2011. Of them, 31 (70%) had an available frozen serum sample collected at the date of LS assessment and were included as cases in the study. These cases were paired with HIV-infected patients, without evidence of active HCV or HBV coinfection, selected from the same cohort with a LS < 7.2 kPa who were matched by age, sex, CD4 cell count and study center.

Laboratory procedures

All plasma samples were tested for the presence of HEV-specific IgG antibodies using both the Wantai HEV-IgG ELISA kit (Beijing Wantai Biological Pharmacy Enterprise CO., LTD., Beijing, China) and the recomWell HEV IgG ELISA (Mikrogen GmbH, Neuried, Germany). Confirmatory testing was performed using the recomLine HEV IgM/IgG immunoassay (Mikrogen GmbH, Neuried, Germany). Samples were analyzed according to the manufacturer's instructions. We defined exposure to HEV as the detection of serum HEV antibodies by at least one of the two ELISA assays, provided that it was confirmed by Immunoblot. A real-time PCR RNA assay was conducted in all plasma samples to identify subjects with active HEV infection.

Statistical analysis

Continuous variables are expressed as median (Q1–Q3). Categorical variables are presented as numbers (percentage). Continuous variables were compared using the Wilcoxon test whereas the frequencies were compared by the McNemar test. Data were analyzed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA).

Ethical aspects

This study has been designed and performed according to the Helsinki declaration and was approved by the Ethics Committee of Hospital Universitario de Valme.

Results

The main features of the study population are depicted in Table 1. Among cases, 8 (26%) patients showed a LS ≥ 14.6 kPa and 9 (29%) had a LS ≥ 9 kPa but <14.6 kPa. Twelve (39%) cases had elevated levels of liver enzymes whereas this was observed in 7 (22%) controls ($p = 0.3$).

Exposure to HEV was demonstrated, according to the criteria used in this study, in 9 (29%) of the cases whereas it was shown in 5 (16%) of the controls ($p = 0.3$) (Table 1). Serum HEV RNA was

Table 1
Features of the study population.

Parameter	Cases ($n = 31$)	Controls ($n = 31$)	*P* bivariate
Age, median (Q1–Q3)	50 (41–60)	49 (46–55)	0.8
Sex			
Male	25 (80)	25 (80)	1.0
Female	6 (20)	6 (20)	
Risk factor			
Heterosexual	19 (61%)	18 (58%)	
Male-to-male	5 (16%)	7 (23%)	0.7
Other	7 (23%)	6 (19%)	
Body mass index, median (Q1–Q3)	26 (23–29)	24 (23–29)	0.1
CD4 cell count, median (Q1–Q3)	451 (165–671)	484 (273–610)	0.1
RNA HIV viral load			
<50 copies/mL	24 (77%)	26 (84%)	0.7
≥50 copies/mL	7 (23%)	5 (16%)	
Alanine aminotransferase, IU/mL	32 (23–51)	27 (20–41)	0.08
Aspartate aminotransferase, IU/mL	29 (23–41)	24 (20–31)	0.04
Exposure to HEV[a]			
Positive	9 (29)	5 (16)	0.3
Negative	22 (71)	26 (84)	

[a] Exposure to HEV was defined as a positive detection of IgG antibodies by one of the ELISA that was further confirmed by the Immunoblot.