Research Article

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Investigation of Hepatitis E Virus Seroprevalence and Chronic Hepatitis E Infection in HIV-Positive Patients

HIV Pozitif Hastalarda Hepatit E Virüs Seroprevelansı ve Kronik Hepatit E Enfeksiyonunun Araştırılması

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ABSTRACT

Objectives: This study aimed to investigate the seroprevalence of hepatitis E virus (HEV) and chronic HEV infection in patients with confirmed human immunodeficiency virus (HIV)-1 infection.

Materials and Methods: This prospective single-center study included a sample of 101 patients aged 18-84 years who were admitted to Hatay Mustafa Kemal University Hospital between May 2022 and December 2022 with a confirmed diagnosis of HIV-1 infection. From the blood samples collected for the study, anti-HEV immunoglobulin M (IgM) [HEV IgM enzyme-linked immunosorbent assay (ELISA), DiaPro, Italy] and anti-HEV immunoglobulin G (IgG) (HEV IgG ELISA, DiaPro, Italy) were evaluated using the microplate ELISA method. Ribonucleic acid (RNA) was extracted from plasma samples using a Qiagen virus kit (Qiagen EZ1 automated system, Germany). HEV-RNA was tested using an in-house reverse transcription polymerase chain reaction for all samples included in the study. In addition, HIV-RNA, CD4+T cell count, hepatitis B surface antigen (HbsAg), anti-hepatitis C virus (HCV), anti-hepatitis A virus (HAV) IgG, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (TBIL), and venereal disease research laboratory (VDRL) parameters were obtained from the hospital automation system.

Results: Anti-HEV IgG seropositivity was 3.96% (n=4). HEV-RNA was analyzed from all samples, but no HEV-RNA positivity was detected. There was no significant difference between the anti-HEV IgG (+) and anti-HEV IgG (-) group in terms of HIV-RNA level, CD4+T cell count, ALT, AST, alkaline phosphatase, gamma-glutamyl

ÖZ

Amaç: Bu çalışmada, insan immün yetmezlik virüsü (HIV)-1 enfeksiyonu doğrulanmış hastalarda hepatit E virüsü (HEV) ve kronik HEV enfeksiyonunun seroprevalansının araştırılması amaçlandı.

Gereç ve Yöntemler: Bu prospektif ve tek merkezli çalışma, Mayıs 2022 ile Aralık 2022 tarihleri arasında Hatay Mustafa Kemal Üniversite Hastanesi'ne HIV-1 enfeksiyonu tanısı doğrulanmış olarak başvuran 18-84 yaş arası 101 hastadan oluşan bir örneklemi içermektedir. Çalışma için alınan kan örneklerinden, mikroplaka kullanılarak anti-HEV immünoglobulin M (IgM) [HEV IgM enzim bağlantılı immünosorbent tahlili (ELISA), DiaPro, İtalya] ve anti-HEV IgG (HEV IgG ELISA, DiaPro, İtalya) ELISA yöntemi çalışıldı. Plazma örneklerinden ribonükleik asit (RNA) ekstraksiyonu, bir Qiagen virüs kiti (Qiagen EZ1 otomatik sistemi, Almanya) kullanılarak gerçekleştirildi. HEV-RNA, çalışmaya dahil edilen tüm numunelerde kurum içi ters transkripsiyon polimeraz zincir reaksiyonu testi kullanılarak test edildi. Ayrıca HIV-RNA, CD4+T hücre sayısı, hepatit B yüzey antijeni (HbsAg), anti-hepatit C virüsü (HCV), anti-hepatit A virüsü (HAV) IgG, aspartat transaminaz (AST), alanin transaminaz (ALT), total bilirubin (TBİL) ve zührevi hastalıklar araştırma laboratuvarı (VDRL) parametreleri hastane otomasyon sisteminden elde edildi.

Bulgular: Anti-HEV IgG seropozitifliği %3,96 (n=4) olarak belirlendi. Tüm örneklerde HEV-RNA analizi yapıldı ancak HEV-RNA pozitifliği saptanmadı. Anti HEV IgG (+) grupla, anti HEV IgG (-) grup arasında HIV-RNA düzeyi, CD4+T hücre sayısı, ALT, AST, alkaline

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transpeptidase, and TBIL levels. Anti-HAV IgG seropositivity was observed in 89.1% (n=90) of the patients included in our study, HbsAg seropositivity was observed in 1.0% (n=1), and HCV seropositivity was not observed. VDRL seropositivity was observed in 11.9% (n=12) of the patients.

Conclusion: Although our findings showed that HEV seroprevalence was not high in HIV-positive patients and did not develop into chronic infection, we believe that multicenter studies with a larger number of patients are needed to investigate the relationship between HIV and HEV in our country.

Keywords: HIV, hepatitis E virus seroprevalence, chronic hepatitis E infection

phosphatase, gama-glutamil transferaz ve TBİL düzeyleri açısından anlamlı fark yoktu. Çalışmamıza dahil edilen hastalarda anti-HAV IgG seropozitifliği %89,1 (n=90), HBsAg seropozitifliği pozitifliği %1,0 (n=1) seropozitifliği gözlendi ancak HCV seropozitifliği görülmedi. VDRL seropozitifliği %11,9 (n=12) görüldü.

Sonuç: Bulgularımız HIV pozitif hastalarda HEV seroprevalansının yüksek olmadığını ve kronik enfeksiyona dönüşmediğini gösterse de ülkemizde HIV ile HEV arasındaki ilişkinin araştırılması için daha fazla sayıda hasta ile çok merkezli çalışmalara ihtiyaç olduğu kanaatindeyiz.

Anahtar Kelimeler: HIV, hepatit E virüs seroprevelans, kronik hepatit E enfeksiyonu

Introduction

Although hepatitis E virus (HEV) infection is a disease that occurs worldwide, its prevalence is higher in the least developedand developing countries (1,2). Although HEV infection usually results in an acute and self-limiting clinical course, pregnancy, young age, chronic liver disease, solid organ transplantation, and human immunodeficiency virus (HIV) infection, and so forth. It can be severe in the high-risk groups. In addition, HEV infection can become chronic in immunocompromised patients (solid organ transplantation, HIV-positive patients with a CD4+T cell count <200 cells/mm^3), and this situation is more common in developed countries (3). Many studies have shown that HEV seroprevalence in HIV-positive patients is different (high, same, and low) compared with the healthy population (4,5,6,7). Many studies on HEV seroprevalence (covering the non-HIV population) have been conducted in Turkey. In a comprehensive meta-analysis of these studies, HEV seroprevalence was reported to be 0-12.4% on average (8). In our literature review, we found that very few studies have investigated the relationship between HEV and HIV in our country. In addition, chronic HEV infection and genotype analysis were not performed in HIV-positive patients. Therefore, large-scale studies are needed. For these reasons, we investigated the seroprevalence of HEV in HIV-positive patients to determine the presence of chronicity and performed HEV genotype analysis.

Materials and Methods

This prospective single-center study included a sample of 101 patients aged 18-84 years who were admitted to Hatay Mustafa Kemal University Hospital between May 2022 and December 2022 with confirmed diagnoses of HIV-1 infection. We included 50 patients whose HIV-1 infection diagnosis was confirmed and who had not yet started treatment and 51 patients whose HIV-1 infection diagnosis was confirmed at least 6 months previously and who were receiving treatment. After obtaining written consent from the patients selected on a voluntary basis, we recorded their demographic and clinical characteristics and laboratory findings.

The inclusion criteria were patients followed up with a diagnosis of HIV-1 and those who provided written consent. Patients younger than 18 years were not included in the study.

We obtained blood samples from the patients; 5 mL was placed in a yellow-capped gel biochemistry tube, and 4 mL was placed in a purple EDTA hemogram tube. The samples were centrifuged within 30 minutes at 4,000 rpm for 10 minute. Serum and plasma samples were separated into Eppendorf tubes and stored at -80 °C until the day of study. All samples were sent to the Ankara General Directorate of Public Health, National HIV/AIDS and Viral Hepatitis Microbiology Reference Laboratory. In this study, anti-HEV immunoglobulin M (IgM) [HEV IgM enzyme-linked immunsorbent assay (ELISA), DiaPro, Italy] and anti-HEV immunoglobulin G (IgG) (HEV IgG ELISA, DiaPro, Italy) were evaluated using the microplate ELISA method. We extracted ribonucleic acid (RNA) from plasma samples using a Qiagen virus kit (Qiagen EZ1 automated system, Germany). HEV-RNA was tested using an in-house reverse transcription polymerase chain reaction test for all samples included in the study. In addition, HIV-RNA, CD4+T cell count, hepatitis B surface antigen (HbsAg), anti-hepatitis C virus (HCV), anti-hepatitis A virus (HAV) IgG, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (TBIL), and venereal disease research laboratory (VDRL) parameters were obtained from the hospital automation system.

Statistical Analysis

We used IBM SPSS Statistics version 22.0 package for thethe statistical analysis of the data. We evaluated the compliance of continuous data with the assumption of normality according to the Kolmogorov-Smirnov test and coefficient of variation. Categorical measurements were given as numbers and percentages, continuous measurements with non-normal distribution were given as median (minimum-maximum) or median (interquartile range: 25th-75th percentiles), and continuous measurements with normal distribution were given as mean and standard deviation. We used Pearson's chi-square test or Fisher's exact test statistics to compare categorical measurements between groups. For the pairwise comparisons of groups, we used the Mann-Whitney U test if the assumptions were not met and the independent-sample (Student) t-test if the assumptions were met. In all the tests, the statistical significance level was set at 0.05.

We conducted this study to investigate HEV seroprevalence and chronic HEV infection in HIV-positive patients. This study was conducted with the permission of the Mustafa Kemal University Faculty of Medicine Clinical Research Ethics Committee (approval number: 2022/52, date: 09.05.2022) and funding provided by Scientific Research Projects (project number: 22.TU.010).

Results

Of the 101 patients diagnosed with HIV-1 included in our study, 78 (77.2%) were male and 23 (22.8%) were female, and the median age was 32 years. We found no significant difference in gender or age between the new diagnosis group and the old diagnosis group (p=0.582 and p=0.257, respectively) (Table 1).

Although anti-HEV IgM positivity was not detected in any of the blood samples and anti-HEV IgG seropositivity was low (3.96%), we analyzed HEV-RNA from all samples. However, HEV-RNA positivity was not detected in any of the samples. Because HEV-RNA positivity was not detected in our study, we could not perform HEV genotype analysis. The reason for testing HEV-RNA in all patients who are anti-HEV IgM and IgG negative, as well as in patients who are anti-HEV IgG-positive, is that these patients are also HIV positive. As is well known, antibodies such as IgM and/or IgG might not be detected in immunosuppressed patients. We applied polymerase chain reaction to all of our patients with the idea that we could detect HEV-RNA in our patients with negative antibodies. Although thethe anti-HEV IgG (+) rate was 13.0% in women, it was 1.3% in men. Of the 50 patients in the new diagnosis group, anti-HEV IgG positivity was detected in two patients (4.0%); among the 51 patients in the old diagnosis group, anti-HEV IgG positivity was detected in 2 (3.9%). Because of the small number of patients, we could not perform significance testing. Table 2 presents a summary of the comparison of demographic and clinical characteristics between anti-HEV IgG-positive and anti-HIV (+) cases.

Table 3 summarizes the laboratory parameters of the anti-HEV IgG-positive and -negative HIV (+) cases. There was no significant difference between the anti-HEV IgG (+) group and the anti-HEV IgG (-) group in terms of HIV-RNA level, CD4+T cell count, ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and TBIL levels (p=0.528, p=0.573, p=0.313, p=0.432, p=0.474, p=0.243, and p=0.413, respectively).

Table 1. Comparison of the age and sex characteristics of the patients

Variables		Total (n=101)	New diagnosis (n=50)	Old diagnosis (n=51)	p-value
Age (year), (median, min.-max.)		32 (19-84)	33 (19-84)	32 (19-67)	0.582*
Gender n (%)	Male	78 (77.2)	41 (82.0)	37 (72.5)	0.257**
	Female	23 (22.8)	9 (18.0)	14 (27.5)	

*Mann-Whitney U test, **Pearson's chi-square test, n: Number, min.: Minimum, max.: Maximum

Table 2. Comparison of demographic and clinical characteristics between anti-HEV IgG-positive and anti-HIV (+) cases

Variables	Anti-HEV IgG (+) (n=4)	Anti-HEV IgG (-) (n=97)	p-value*
Age, year	56.0 (47.5-62.0)	32.0 (27.0-42.0)	0.011
Sex, n (%)			
Male Female	1 (25.0) 3 (75.0)	77 (79.3) 20 (20.7)	0.002
Newly diagnosed HIV (+) cases, n (%)	2 (50.0)	48 (49.5)	0.984
Foreign nationals, n (%)	0 (0)	7 (7.2)	0.578
MSM + bisexuality, n (%)	0 (0)	44 (45.4)	0.073
Education level (High School/University), n (%)	1 (25.0)	61 (62.9)	0.127
Additional disease, n (%)	1 (25.0)	11 (11.3)	0.408
Smoking, n (%)	1 (25.0)	40 (39.6)	0.517
Alcohol use, n (%)	0 (0)	28 (28.9)	0.206
Foreign travel history, n (%)	0 (0)	11 (11.3)	0.476
Coinfection rate, n (%)			
Anti-HAV IgG (+) HBsAg (+) VDRL (+) Anti-HCV (+)	2 (50.0) 0 (0) 0 (0) 0 (0)	88 (90.7) 1 (1.0) 14 (14.4) 0 (0)	0.010 0.838 0.413
CD4+T cell status			
<200 cells/µL 200-499 cells/µL ≥500 cells/µL	0 (0) 3 (75.0) 1 (25.0)	7 (7.2) 70 (72.2) 20 (20.6)	0.849

Continuous measurements that did not comply with normal distribution were expressed as median (interquartile range: 25th-75th percentiles).
n: Number, HIV: Human immunodeficiency virus, MSM: Man who have sex with man, anti-HAV IgG: Hepatitis A virus antibody test immunoglobulin G, HBsAg: Hepatitis B surface antigen, VDRL: Venereal disease research laboratory, anti-HCV: Hepatitis C virus antibody test, anti-HEV: Hepatitis E virus antibody test, *Pearson's chi-square test vena Fisher's exact test

One of the 101 patients included in our study (1.0%) was HbsAg-positive. This patient was in the new diagnostic group. In our study, none of the patients tested positive for anti-HCV antibodies. In our study, anti-HAV IgG was positive in 90 (89.1%) patients. Anti-HAV IgG was positive in 44 (88.0%) patients in the new diagnosis group and in 46 (90.2%) patients in the old diagnosis group. No significant difference was detected between the groups in terms of anti-HAV IgG positivity (p=0.723). In our study, 12 (11.9%) patients were VDRL-positive. VDRL positivity was detected in seven (14.0%) patients in the new diagnostic group and in five (9.8%) patients in the old diagnostic group. We found no significant difference between the groups regarding VDRL positivity (p=0.515). Table 4 presents a comparison of hepatitis co-infection and VDRL test results between the patient groups.

Discussion

In the HEV seroprevalence study conducted in our country with 114 HIV-positive volunteers at Sakarya University in 2019, seropositivity was reported to be 4%, which is similar to our study (9). In addition, although all anti-HEV IgG-positive patients in that study were male, in our study the anti-HEV IgG (+) rate was 13.0% in females and 1.3% in males. In another study conducted in Uganda, the authors found anti-HEV IgG seropositivity found to be similar between volunteers with and without HIV, and they reported that there was no difference in age gender distribution (7). In studies conducted in our country and in Uganda, the median age of anti-HEV IgG (+) cases was similar to that of the anti-HEV IgG (-) group, being significantly higher. The reason for the high age in the studies conducted in our country and Uganda might be due to the high probability of encountering HEV over time due to fecal-oral transmission.

A study conducted in HIV-negative volunteers [including HIV-negative men who have sex with men (MSM)] in Italy showed that sexual transmission of HEV was unlikely and had no impact on HEV prevalence (10). In another study conducted in the Netherlands, the authors reported that there was no significant relationship between MSM sexual habit and HEV seropositivity in HIV-positive patients (11). In our study, we did not detect HEV in individuals with MSM sexual habits, which supports the findings of studies conducted in Italy and the Netherlands.This might be because of the lack of sexual transmission of HEV.

There are also studies in the literature investigating anti-HEV IgG seropositivity in HIV-positive pregnant women (12,13). The fact that anti-HEV IgG was found to be negative in all three pregnant patients in our study can be explained by the small number of patients. To determine the level and/or relationship of HEV seropositivity, especially in HIV-positive pregnant women in Turkey, further studies are needed. We recommend that multicenter studies with a higher number of patients be conducted in Turkey to determine the relationship between HEV seropositivity levels, especially in HIV-positive pregnant women.

In addition, in our study, we investigated the seroprevalence of VDRL, HbsAg, anti-HCV, and anti-HAV IgG in HIV-positive patients, and the results we found were similar to those of another study conducted in our country (14). However, further studies with larger patient series are required to clarify this issue.

Table 3. Comparison of laboratory parameters between anti-HEV IgG-positive and anti-HIV (+) cases

Variables	Anti-HEV IgG (+) (n=4)	Anti-HEV IgG (-) (n=97)	p-value
HIV-RNA (copies/mL)	10115 (0-50119)	0 (0-346100)	0.528
CD4+T number, cells/µL	404.5 (357.5-514.5)	398.0 (300.0-452.0)	0.573
AST, U/L	17 (13.5-27.5)	24 (16-31)	0.313
ALT, U/L	20 (14.5-29.0)	25 (18-33)	0.423
ALP, U/L	100.5 (73.5-130.5)	112 (96-129)	0.474
GGT, U/L	37 (30.5-47.5)	31 (23-40)	0.243
TBIL, mg/dL	0.125 (0.115-0.165)	0.180 (0.110-0.210)	0.413

Continuous measurements that did not comply with normal distribution were expressed as median (interquartile range: 25th-75th percentiles).
Anti-HEV IgG: Hepatitis E virus antibody test immunoglobulin G, HIV-RNA: Human immunodeficiency virus-ribonucleic acid, AST: Aspartate aminotransferase, ALT: Alkaline aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, TBIL: Total bilirubin

Table 4. Comparison of hepatitis co-infection and VDRL test results between patient groups

Variables		Total (n=101)	New diagnosis (n=50)	Old diagnosis (n=51)	p-value*
HBsAg n (%)	Positive	1 (1.0)	1 (2.0)	0 (0.0)	0.495
	Negative	100 (99.0)	49 (98.0)	51 (100.0)	
Anti HCV n (%)	Positive	0 (0.0)	0 (0.0)	0 (0.0)	-
	Negative	101 (100.0)	50 (100.0)	51 (100.0)	
Anti-HAV IgG n (%)	Positive	90 (89.1)	44 (88.0)	46 (90.2)	0.723
	Negative	11 (10.9)	6 (12.0)	5 (9.8)	
VDRL n (%)	Positive	12 (11.9)	7 (14.0)	5 (9.8)	0.515
	Negative	89 (88.1)	43 (86.0)	46 (90.2)	

n: Number, *Pearson's chi-square test vena Fisher's exact test, HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virüs, HAV: Hepatitis A virüs, VDRL: Venereal disease research laboratory

In our study, the fact that anti-HEV IgG (+) was not found in any of the seven (6.9%) HIV (+) cases with a CD4+T cell count <200 cells/μL is incompatible with the literature. In contrast, studies conducted in various countries around the world have reported a correlation between HIV and HEV seroprevalence, but this correlation was independent of the CD4+T cell count. For example, a study involving 251 HIV-positive patients in Iranfoundno relationship between CD4+T cell count and HEV seropositivity (4). Similarly, in a study conducted in China with 639 HIV-positive cases, the authors found that HEV seropositivity (39.4%) was higher than that in the healthy population (15). In our study, the fact that we did not find anti-HEV IgG (+) in any of the seven cases with a CD4+T cell count <200 cells/μL is, in our opinion, due to the small number of cases.

In our study, the anti-HEV IgG (+) level was significantly higher in the anti-HEV IgG (-) group than in the anti-HEV IgG (+) group (90.7% and 50%, respectively, p=0.010), which is similar to a study conducted in our country (9). The seroprevalence of HAV and HEV is strongly associated with socioeconomic conditions and similar transmission routes (fecal-oral), especially due to war, natural disasters, and so forth, as well as migration from developing countries to developed countries. It has been suggested thatcher HAV and HEV seroprevalence is likely to increase in developed countries (16). In our study, our finding that anti-HEV IgG (+) levels were significantly higher in the anti-HEV IgG (-) group than in the anti-HEV IgG (+) group is important. This situation raises the question of whether cross-immunity against HEV infection occurs in those who have previously had an HAV infection. The second question is whether anti-HAV IgG protects against HEVs or not in cross-immunity. Considering the ages at which these two infections were acquired, it is more likely that HAV infection was acquired in childhood in both our country and other countries around the world, and anti-HAV IgG positivity is protective against HEV. However, because of the small number of individuals with positive anti-HEV IgG antibodies in our study, this argument remains weak. In other words, in this study conducted in Hatay, comprehensive studies are needed to understand whether anti-HAV IgG seropositivity is inversely proportional to anti-HEV IgG seropositivity.

We found no significant difference in HIV-RNA levels, CD4 count, ALT, AST, ALP, GGT, and TBIL levels between the anti-HEV IgG (+) group and the anti-HEV IgG (-) group, and this result is similar to that of another study conducted in our country (9).

Studies conducted in immunosuppressed patients or those receiving chemotherapy/immunotherapy due to immunosuppression (e.g., solid organ transplantation, bone marrow transplantation, lymphoma) have demonstrated the presence of chronic HEV infection. Although studies have shown that HEV infection becomes chronic in HIV-positive patients, this phenomenon remains a mystery. In these studies, chronic HEV infection was found to be predominantly associated with genotype 3, but some studies have shown that genotypes 4 and genotype 7 also cause chronic infection (17,18,19,20). Chronic HEV infection has not been investigated in HIV-positive patients in our country. Although one of the most important aims of our study was to investigate chronic HEV infection in HIV-positive patients and perform genotype analysis, chronic HEV infection was not detected, and genotype analysis could thus not be performed. Although our study has some limitations, our findings suggest that HEV does not become chronic in HIV-positive patients and does not pose a problem for these patients, and more studies are needed.

Study Limitations

The small number of patients and data obtained from a single center is among the limitations of this study.

Conclusion

We conducted this study to investigate HEV seroprevalence in HIV-positive patients, determine whether HEV develops into a chronic infection, and perform genotype analysis. We found that the HEV seropositivity (anti-HEV IgG) was low at a rate of 3.96%. Although anti-HEV IgM was negative and anti-HEV IgG was positive at a low rate in all patient samples, we studied HEV-RNA in all samples and did not detect HEV-RNA positivity in any of the samples. Therefore, we could not perform genotype analysis. Our results show that HEV seroprevalence is low in HIV-positive patients, there is no evidence of chronic infection, and this does not pose a problem for HIV-positive patients. To investigate the relationship between HIV and HEV in our country, more studies with a larger number of patients are needed. In addition, we propose that studies should be conducted to investigate the seroprevalence of VDRL, HbsAg, anti-HCV, and anti-HAV IgG in HIV-positive patients as secondary results in our study, and these patients should be treated, followed up, and vaccinated if necessary.

Ethics

Ethics Committee Approval: This study was conducted with the permission of the Hatay Mustafa Kemal University Faculty of Medicine Clinical Research Ethics Committee (approval number: 2022/52, date: 09.05.2022).

Informed Consent: Informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: H.Y., Y.Ö., M.Ç., T.D., Concept: H.Y., Y.Ö., M.Ç., T.D., Design: H.Y., Y.Ö., T.D., Data Collection or Processing: H.Y., M.Ç., Analysis or Interpretation: H.Y., M.Ç., Literature Search: H.Y., Y.Ö., M.Ç., T.D., Writing: H.Y., Y.Ö., M.Ç., T.D.

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