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Sero - Epidemiology of Hepatitis E and D Infections among HIV - Infected and HIV/HCV - Coinfected Patients in Jahrom, Southern Iran

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Abstract

Background: Co - infection of hepatitis E virus (HEV) and hepatitis D virus (HDV) in human immunodeficiency virus (HIV) infected patients can develop and increase hepatic complications in the world, particularly in developing countries.
Objectives: The purpose of this study was to assess and compare the sero - virological prevalence of HEV and HDV in patients bearing HIV infection and HIV/HCV co - infection, as well as their relation to clinical and demographic data.
Methods: Cross - sectional study testing IgM/IgG anti - HEV and total antibodies HDV in serum samples belong to 73 HIV infected patients and co - infected HIV - HCV patients were evaluated. Demographic, lifestyle, and laboratory data such as CD4 counts and viral load were prospectively collected on each patient with the HIV infection.
Results: There were 26 HEV infected patients IgG positive, two HEV infected patients IgM positive, two HDV infected patients total antibodies positive, and only one HDV infected patient IgM among the 73 HIV infected patients. The prevalence of HDV positive IgG and total anti - HDV among co - infected patients were 2.2% and 2.2%. In addition 18 (69.2%) and 2.2% were positive for anti - HEV IgG and IgM, respectively. Furthermore, HIV viral load among HIV co - infected patients with HEV or HDV were shown higher compared to patients solely infected with only HIV. Also, the numbers of HEV or HDV positive were high in low levels of CD4.
Conclusions: According to the results, frequency of occurrence of hepatitis E was higher than hepatitis D in HIV infected patients. Severity of HIV infection and liver damage caused by HEV and HDV infections were in a direct relationship. Hence, HIV and HCV screening should be implemented in HIV - infected patients with liver damage.

Keywords: HEV, HDV, Co - infection, HIV

1. Background

Hepatitis E virus (HEV) infection is one of the main causes for endemically - transmitted acute hepatitis throughout the world (1). This virus is a positive sense single - strand RNA virus without envelop that is classified to four genotypes. The HEV infection 1 and 2 genotype are circulating into developing countries, while the HEV infection 3 and 4 genotypes are endemically detected in the Europe and Unites States; each infection has distinct clinical and epidemiological characteristics (2, 3). The HEV infection leads to a severe fulminate hepatitis if the infection happens in the late of a pregnancy (4).

Hepatitis D virus (HDV), or the Delta virus, is a defective RNA satellite virus that its infectivity is dependent on the hepatitis B virus (HBV) (5). Capsid of HDV consists of two proteins: small HDAg (S - HDAg) and large HDAg (L - HDAg) (6). In addition, HDV was divided into eight genotypes (5). Transmission of HDV can observe either via simultaneous infection with HBV or superimposed on hepatitis B virus (6). Chronic hepatitis C virus (HCV) is a rapidly progressing infection where different HCV genotypes leads to liver disease and its dangerous symptom is hepatocellular carcinoma (HCC) (7). On the other hand, different risk factors such as HIV infection and cellular factors can be affected on the symptoms (8-10). Some studies have been shown that the HDV pathology is various and an ongoing debate to research: for example, HDV does not have any direct CPE due to the fact that transplantation of the infected liver with HDV expresses HDAg without any liver damage (11).

Prevalence and progression to chronicity of HEV and HIV infections could be higher than what is expected (12)

and that this condition is was happened in high risk individuals (13). High - accelerate liver fibrosis progression and worse prognosis were shown among patients with previous liver damage who were later infected with HEV (14, 15). In HIV - infected communities, chronic HEV infection has been characterized as an emerging cause of liver fibrosis/cirrhosis in patients without HCV or HBV co - infection (16, 17). Chronic liver cirrhosis and inflammation were reported among HIV co - infected patients with HDV (18, 19). In addition, HDV co - infected patients with HBV were shown progressive liver cirrhosis compared to HDV infected patients (20).

In Iran, previous studies have been examined by only one of the co - infections HIV with HEV or HDV. Thus, in a study in 2013 by Aghasadeghi et al., it was reported that the HDV infection in patients infected with HIV was among undergoing hemodialysis (21). In another study in Bushehr (South of Iran), Naeimi et al., showed positive serological cases for HEV among blood donors (22). Since there is not much data available on sero - epidemiology of co - infections HIV with HEV or HDV among community, this research was performed in order to better understand this co - infection among regional community.

2. Objectives

The current study was to determine the seroprevalence anti - HEV and HDV antibodies among HIV infected and HIV/HCV - coinfected patients, as well as the antibodies prevalence and their relation to clinical and demographic characteristics.

3. Methods

This cross - sectional study was designed based on HIV patients that were selected from Jahrom University of Medical Sciences for diagnosing HIV and viral load testing in the year of 2015. In this study, patients were classified to three groups: HIV mono (group I), HIV/HEV co - infections (group II), and HIV/HDV co - infections (group III). Stored EDTA - plasma samples (- 80°C) were used for HEV specific IgM and IgG antibodies, and also detected HDV IgM and total antibodies in plasma. Enzyme - linked Immunosorbent Assay (ELISA) (Wantai, Beijing,China) test were used according to the manufacturer's instructions. In addition, serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT) levels were determined. All the outcomes were analyzed using the SPSS version 18.1. Categorical variables were expressed as number of cases (percentage) and compared using the Fisher's exact test. Continuous variables were expressed in mean $\pm$ SD and compared using unpaired Student's *t* - tests. Statistical significance was defined at P values of < 0.05. Ethical approval for the current study was obtained from the Ethical Review Board in Jahrom University of Medical Sciences.

4. Results

The 73 HIV infected patients were identified and their clinical characteristics were shown in Table 1. The majority of HIV - infected patients were among 30 - 39 years old (N = 48, 65.8%). HEV and HDV serology results in HIV patients are shown in Table 2. The prevalence of positive HDV among HIV-infected individuals were 1.4% (N = 1) for IgM and 2.8% for total anti - HDV; those were comprised of one (64 years) females and one (55 years) males.

ALT level among group II patients anti - HEV IgG positive was higher than ALT level among group II patients IgG negative ($P < 0.0001$), as well as HEV IgM positive patients were shown higher ALT level than HEV infected patients with IgM negative ($P = 0.037$) (Table 3). The rate of positive anti - HEV IgG individuals among group II patients with CD4 < 250 were higher than patients with CD4 ≥ 250 in this group, this difference was significant ($P < 0.0001$). The HIV viral load among group II patients was significantly higher than viral load among group I patients ($P = 0.007$), however, there was no significant difference between anti - HEV IgG positive with Anti - HEV IgM positive patients. In addition, the HIV viral load among group II patients with the HCV infection were significantly higher than the viral load among group I patients, however, this difference was not seen with co - infected group III patients with HCV infection (data not shown).

Table 4 showed only two positive anti - HDV infected patients among the 73 HIV infected patients. The ALT level in group III patients were significantly higher than group I patients ($P = 0.016$). In addition, the average of HIV viral load among group III patients was $(29.50 \pm 7.77) \times 10^5$) higher than group I patients ($(21.60 \pm 20.27) \times 10^5$). Of course, the average of viral load among co - infected HIV/HCV patients with positive anti - HDV IgM and HDV total antibodies was lower than positive anti - HEV IgG and IgM patients. Table 5 shows that the ALT level in patients with positive anti - HDV total antibodies was higher than positive anti - HEV IgG patients; this difference was significant ($P = 0.015$).

5. Discussion

Anti - HDV and anti - HEV antibodies were identified active and as previous infections that can be used to study the

Table 1. Clinical, Biochemical, and Immunologic Features of 73 HIV - infected Patients

Variables	Number (%)
Gender	
Male	53 (72.6)
Female	20 (27.4)
Age[a]	36 ± 2.1
20 - 29	15 (20.5)
30 - 39	48 (65.8)
40 - 49	7 (9.6)
> 50	3 (4.1)
HCV treatment	
Yes	45 (61.6)
No	28 (38.4)
HIV/HCV co - infection	45 (61.6)
CD4+ T cell/μL	
≥ 250	46 (63)
< 250	27 (37)
HIV treatment	
Yes	47 (64.4)
No	26 (35.6)
HIV load (IU/mL)[a]	(21.81 ± 20.05) ×10^5
ALT ± SD (IU/L)[a]	39.97 ± 19.84
AST ± SD (IU/L)[a]	34.09 ± 10.67
Education	
Illiterate	22 (30.1)
Primary & secondary	37 (50.7)
High school	7 (9.6)
College	7 (9.6)
Marriage	
Married	60 (82.2)
Single	13 (17.8)
Resident	
Urban	62 (84.9)
Rural	11 (15.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus.
[a] Data was expressed as Mean ± SD.

Table 2. HEV and HDV Serology Results in 73 HIV - Infected Patients

Variables	Positive (%)	Negative (%)
Anti - HEV IgM	2 (2.7)	71 (97.3)
Anti - HEV IgG	26 (35.6)	47 (64.4)
Anti - HDV IgM	1 (1.4)	72 (98.6)
Anti - HDV total	2 (2.7)	71 (97.3)

HEV and HDV epidemiology. Previous HDV and HEV studies have reported the presence of HEV and HDV infections in different regions of the Iran (13, 22); however, there is not enough information regarding HIV co - infection in the Iran. In another study, HIV infected patients has also been reported a low anti - HDV prevalence in the Iran, however, the number of patients is increasing (21).

The finding of the present study showed that ALT mean levels among group II and group III patients were higher than that among group I patients. The progression in the liver cirrhosis and damages was caused by increasing ALT levels (23, 24). HEV and HDV infections cause increased ALT levels, thus, developing liver cirrhosis. Moreover, results were reported that active HDV and HEV infections were an increased risk of liver cirrhosis compared to chronic HDV and HEV infections. In addition, raised anti- and proinflammatory cytokine levels during acute HEV infection correlated with ALT levels (25). Therefore, ALT released from the damaged liver cells causes development of liver tissue destruction. In addition, in the present study, ALT mean levels in HIV, HCV, and HEV co - infection patients was higher due to HCV increased distraction of tissue of the liver; however, this difference was not significant.

HIV viral load and HEV/HDV antibodies presence among patients were in a direct relationship that was similar with previous studies (26). In addition, HIV load level in group II patients was higher than group I patients. In addition, among HCV, HIV, and HEV co - infected patients, HIV viral load significantly increased. In order to support the former result, most patients from group II and III were included in untreated HIV infected patients. Although all of the patients were HIV infected, however HEV and HDV infections were reported more among active HIV infected patients with higher ALT levels. However, in another study there was no difference in anti - HEV seroprevalence between patients with HIV infection and control subjects (27). Analysis of CD4 count showed that the majority of II and III group patients had CD4 < 250. Mentioned outcomes that indicated immune system suppression by HIV infection was caused to increase the risk of HEV and HDV infections as well as liver cirrhosis that was against some previous studies (28). Among group II patients, the rate of anti - HEV IgG was higher than HIV, HCV, and HEV co - infection patients. The presence of HCV cause changes in the host immune system and reduce humoral immunity, therefore, co - infection of these patients with HCV probably cause a reduced immune system against the HEV infection.

This discrepancy was attributed to the regional differ-

Table 3. The Characteristics of the Adult HIV Patients Based on HEV IgG and IgM Status

Characteristics	Anti - HEV IgG			Anti - HEV IgM		
	Positive (%)	Negative (%)	P Value[a]	Positive (%)	Negative (%)	P Value[a]
No.	26 (35.6)	47 (64.4)		2 (2.7)	71 (97.3)	NS
Age, y			< 0.0001			
20 - 29	0 (0)	15 (31.9)		0 (0)	15 (21.1)	
30 - 39	25 (96.2)	23 (48.9)		2 (100)	46 (64.8)	
40 - 49	0 (0)	7 (14.9)		0 (0)	7 (9.9)	
> 50	1 (3.8)	2 (4.3)		0 (0)	3 (4.2)	
Gender			NS			NS
Male	17 (65.4)	31 (76.6)		2 (100)	51 (71.8)	
Female	9 (34.6)	11 (23.4)	NS	0 (0)	20 (28.2)	
ALT ± SD (IU/L)[c]	58.61 ± 22.93	29.65 ± 5.04	< 0.0001[c]	79 ± 35.35	38.87 ± 18.50	0.037[b]
AST ± SD (IU/L)[c]	33.92 ± 14.20	34.19 ± 8.28	NS[c]	36 ± 0.00	34.04 ± 10.82	NS[b]
HCV treatment			NS			NS
Yes	18 (69.2)	27 (57.4)		2 (100)	43 (60.6)	
No	8 (30.8)	20 (42.6)		0 (0)	28 (39.4)	
HIV treatment			NS			NS
Yes	19 (73.1)	28 (59.6)		2 (100)	45 (63.4)	
No	7 (26.9)	19 (40.4)		0 (0)	26 (36.6)	
CD4+T cell/μL			< 0.0001			NS
≥ 250	5 (19.2)	41 (87.2)		0 (0)	46 (64.8)	
< 250	21 (80.8)	6 (12.8)		2 (100)	25 (35.2)	
HIV load (IU/mL)[c]	$(29.23 \pm 17.71) \times 10^5$	$(13.07 \pm 22.10) \times 10^5$	0.007[b]	$(30.50 \pm 6.36) \times 10^5$	$(21.57 \pm 20.27) \times 10^5$	NS[b]
Education			NS			NS
Illiterate	9 (34.6)	13 (27.7)		1 (50)	21 (29.6)	
Primary & secondary	13 (50)	24 (51.1)		1 (50)	36 (50.7)	
High school	2 (7.7)	5 (10.6)		0 (0)	7 (9.9)	
College	2 (7.7)	5 (10.6)		0 (0)	7 (9.9)	
Marriage			NS			NS
Married	22 (84.6)	38 (80.9)		1 (50)	59 (83.1)	
Single	4 (15.4)	9 (19.1)		1 (50)	12 (16.9)	
Resident			NS			NS
Urban	22 (84.6)	40 (85.1)		2 (100)	60 (84.5)	
Rural	4 (15.4)	7 (14.9)		0 (0)	11 (15.5)	

Abbreviation: NS, non - significant.
[a] Comparison categorical variables using Fisher's exact test.
[b] Data was expressed as Mean ± SD.
[c] P Values were calculated using unpaired Student's *t* - tests (Continuous variables).

ences in HEV prevalence in different countries: owing to endemic characteristics and high-accelerated HEV prevalence in the developing countries (29), liver cirrhosis had a high progression rating. Transmission route of HEV is oral fecal (30) and difference with transmission of HCV and HBV as well as being unknown of rate of HEV infection in population of developing countries have caused increasing of prevalence of HEV. HIV co - infected patients with HDV were shown higher liver cirrhosis (31). It was related to the presence of the HBV as a crucial factor in this co -

Table 4. Characteristics of Adult HIV Patients According to Anti - HDV Total Status

Characteristics	Anti - HDV Total		
	Positive (%)	Negative (%)	P Value[a]
No.	2 (2.7)	71 (97.3)	
Age, y			NS
20 - 29	0 (0)	15 (21.1)	
30 - 39	2 (100)	46 (64.8)	
40 - 49	0 (0)	7 (9.9)	
> 50	0 (0)	3 (4.2)	
Gender			NS
Male	2 (100)	51 (71.8)	
Female	0 (0)	20 (28.2)	NS
ALT ± SD (IU/L)[b]	101.5 ± 3.53	38.23 ± 17.13	0.016[c]
AST ± SD (IU/L)[b]	30 ± 8.48	34.21 ± 10.75	NS[c]
HCV treatment			NS
Yes	2 (100)	43 (60.6)	
No	0 (0)	28 (39.4)	
HIV treatment			NS
Yes	1 (50)	46 (64.8)	
No	1 (50)	25 (35.2)	
CD4+ T cell/μL			NS
≥ 250	0 (0)	46 (64.8)	
< 250	2 (100)	25 (35.2)	
HIV load (IU/mL)[b]	$(29.50 \pm 7.77) \times 10^5$	$(21.60 \pm 20.27) \times 10^5$	NS[c]
Education			NS
Illiterate	0 (0)	22 (31)	
Primary & secondary	2 (100)	35 (49.3)	
High school	0 (0)	7 (9.9)	
College	0 (0)	7 (9.9)	
Marriage			NS
Married	2 (100)	58 (81.7)	
Single	0 (0)	13 (18.3)	
Resident			NS
Urban	2 (100)	60 (84.5)	
Rural	0 (0)	11 (15.5)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NS, non - significant.
[a] Comparison categorical variables using Fisher's exact test.
[b] Data was expressed as Mean ± SD.
[c] P Values were calculated using unpaired Student's *t* - tests (Continuous variables).

infection. In this study, group II patients were compared with group III. The majority of parameter had no significant difference, however, only the ALT of group III patients was significantly higher than group II patients. Due to this, HDV infected patients had multiple co - infections of HIV and HCV, which caused increase of destroying the liver tissue (9, 32). However, the rate of prevalence of HEV was significantly higher than HDV infection, probably one of the reasons being endemic of HEV in Iran.

This investigation was indicated the most infected pa-

Table 5. Comparison of Impact of Some Important Variables on Positive Anti - HEV IgG and anti - HDV Total Antibodies Patients in HIV Infection

Variables	HIV/Anti - HDV Total Positive	HIV/Anti - HEV IgG Positive	P Value
CD4+ T cell/μL	Number	Number	NS[a]
CD4 $\geq$ 250	0	5	
CD4 < 250	2	21	
ALT $\pm$ SD (IU/L)[b]	101.5 $\pm$ 3.53	58.61 $\pm$ 22.93	0.015[c]
AST $\pm$ SD (IU/L)[b]	30 $\pm$ 8.48	33.92 $\pm$ 14.20	NS[c]
HIV load (IU/mL)[b]	(29.50 $\pm$ 7.77) $\times 10^5$	(29.23 $\pm$ 17.71) $\times 10^5$	NS[c]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NS, non - significant.
[a] Comparison categorical variables using Fisher's exact test.
[b] Data was expressed as Mean $\pm$ SD
[c] P Values were calculated using unpaired Student's *t* - tests (Continuous variables).

tients belonged to low levels of literacy section and urban residents, which some previous studies approved (33). Thus, the absence of enough information about endemic HEV, the low level of public awareness about disease and its transmission like HEV transmission through the fecal - oral, don't have enough information about co - infection HDV and HBV, and does not check HDV in HBV infected patients were the main reasons for high prevalence among the population. Generally, the study indicated prevalence of HIV co - infection with HDV or HEV was considerable.

The higher liver damage was reported among group III patients or group II patients compared to group I patients, it was attributed to weak immune system and high ALT levels among patients. Many studies have suggested that acute HEV was considered a subclinical and self - limiting disease (34); however, co - infection of HEV with HIV cause chronicity of HEV infection and the period of time in which fibrosis progression occurred was alarmingly short. Thus, in co - infection HEV with HIV, progression to cirrhosis may be even faster than descried in HBV or HCV/HIV co - infection (35). Early diagnosis of HIV and HEV co - infection and starting antiviral therapy can lead to reduce clinical complications and hazardous consequences for the patient and clear HEV. Due to interfering between HDV with replication of HBV (36), HDV infected patients were shown as a failure to identify HBV individuals. Medical teams can take appropriate treatment and diagnosis for HEV and HDV infections by having enough information about disease prevalence and characteristics. Moreover, the medical team should investigate not only HCV and HBV but also HEV and HDV.

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