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ORIGINAL ARTICLE

Hepatitis D Virus Infection among HIV-HBV Co-Infected Patients in Kermanshah, West of Iran

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Background and Aims: **There are limited data on the prevalence of viral hepatitis in human immunodeficiency virus (HIV) infected individuals. Comorbid illnesses in patients infected with HIV are of great interest due to their association with poor outcomes and failure of antiretroviral therapy. This study evaluated the prevalence of coinfection by HIV and viral hepatitis D in an endemic area for HIV and hepatitis B in Kermanshah.**

Methods: **We conducted a cross-sectional study in which serological markers for hepatitis B and D viruses were tested in a consecutive sample of all patients referred for treatment of HIV or acquired immunodeficiency syndrome (AIDS). Important variables such as age, gender, origin and exposure category were obtained from existing medical records and from the sexually transmitted diseases and AIDS surveillance database.**

Results: **Among the 888 subjects studied, the prevalence of chronic hepatitis B carriers was 6.4%; the rate of past infection was 40.2%. The presence of hepatitis B was associated with birth in hyperendemic areas of Kermanshah, male sex and illicit drug abuse. The prevalence of hepatitis B, C and D among patients with HIV or AIDS in Kermanshah was lower than that observed elsewhere and is probably associated with the local epidemiology of these viruses and the degree of overlap of their shared risk factors.**

Conclusions: **The prevalence rate for HIV and co-infection with hepatitis D virus found in this study was much lower than those reported elsewhere. An opportunity presents itself to evaluate the prevention of hepatitis D and C through harm reduction.**

Keywords: **HDV, HIV, HBV, Co-Infection, Viral Hepatitis**

Introduction

Hepatitis D virus (HDV) is one of the most unusual pathogens in nature, as it can only infect hepatocytes in the presence of a helper virus-usually hepatitis B virus (HBV). Strictly speaking, HDV is not a virus, itself. Owing to its helper requirement, HDV does not satisfy the definition of a virus and should be called a 'subviral' agent. In addition, as it shares no sequence similarity to the genome of its helper virus, it should be regarded as a "satellite" of HBV. In full, HDV should be termed a subviral satellite agent with HBV-its natural helper virus [(1)]. Therefore HDV is a viral parasite and cannot reproduce or infect in the absence of HBV. It is found only in the cells of patients who are positive for hepatitis B surface antigen (HBsAg). The risk of getting severe liver disease increases in the presence of HDV. Patients are simultaneously infected with HBV and HDV; the disease is self-limited and only 2% of patients will progress to chronic infection. It is interesting to emphasize that the first evidence for the probable existence of HDV dated back to 1978 when a previously-unrecognized intranuclear antigenic material was detected by immunofluorescence in liver biopsies from Italian patients with chronic HBV infection. At first, it was

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thought to be another antigenic specific for HBV, nonetheless, the antigen was eventually shown to be associated with the capsid protein of a previously-unrecognized virus. Subsequently, it was called "hepatitis delta virus" [2].

Co-infections with viral hepatitis in individuals living with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) are of great interest due to their association with unfavorable outcomes and failure of antiretroviral therapy [3-6]. Clinical studies conducted in Europe [6] and in the United States [7] among patients co-infected with HBV indicated an inadequate response to antiretroviral drugs and the development of liver disease.

These unfavorable outcomes and advanced liver disease occur particularly in cases of hepatitis C virus (HCV) co-infection, which is probably attributed to the changes in the natural history of HCV infection in co-infected individuals [4, 8, 9]. No data are available on the prevalence of co-infection in patients with HIV/AIDS in Kermanshah, West of Iran. Since all of these hepatitis viruses share the same transmission mechanisms, high rates of co-infection are expected in all of the endemic regions. Therefore, to estimate the prevalence of co-infection of HIV with HDV and other hepatitis viruses, using data from the routine screening of patients from the only referral clinic for HIV/AIDS in the region, we conducted this study in Kermanshah. In addition to estimate the prevalence of hepatitis in HIV-infected patients, we also performed this research to study the phenomenon of viral interference in HIV-infected patients with hepatitis B,C, or D.

Materials and Methods

In this cross-sectional study, we included all HIV-infected patients, from January to November 2007, visited in Kermanshah triangular clinic which is the only referral center for behavioral diseases (HIV/AIDS, addiction, sexually transmitted diseases (STDs)) who were also anti-HBs-Ag positive using a census method sampling. The center is located in a university-based public health service and provides comprehensive medical care to HIV-infected adults. For each patient, we reviewed demographics, risk factors for HIV infection, highly active antiretroviral therapy (HAART) received, current or prior use of lamivudine, current CD4 cell count, and liver function tests.

The variables studied included gender, age, place of birth, HIV exposure category, and results from HBV, and HDV tests. Those whose medical charts reported AIDS-related symptoms were considered to have AIDS. Tests were performed using the enzyme-linked immunosorbent assay (ELISA) in accordance with the manufacturer's recommendations. Specimens with confirmed HBs-Ag^+ or seropositive for IgG antibody to hepatitis B core antigen (anti-HBc IgG^+) were tested with anti-HDV antibody. HIV/AIDS patients were classified according to their co-infection status as follows: chronic HBV carriers (HBs-Ag^+), past infection (only anti-HBc^+) and HDV co-infection (anti-HDV^+). Association between independent factors and co-infection was evaluated using the Fisher's exact tests using Epi-Info ver 2002. Confidence interval (CI) was 95% and *P* value <0.05 was considered statistically significant.

Results

From January to November 2007, 888 (870 male and 17 female) HIV-infected patients were investigated. The mean± SD age of participants was 30.7±7.6 years. The minority (4.7%) was employed; 45.6% had temporary job, or had mainly illegal sources of income (49.7%) like drug dealing, prostitution, *etc*. About 54% of the injection drug users (IDUs) had lower than high school education. Most participants reported a history of former imprisonment (50% with one to four and 23.5% with more than five occasions). Among the subjects, only four (5%) reported sharing injections while in prison. Respectively, 53.5% and 46.8% of the subjects lived in a middle-class and low-income families.

The most frequently injected drug was heroin (96.2%), followed by cocaine (4%); the latter was generally used during trips abroad. Other illicit drugs such as injectable or non-injectable amphetamine derivatives, solvents and tranquilizers were also consumed. The mean±SD age at first injection was 19.6±5.2 years, and the mean±SD duration of IV drug abuse was 13.9±8.8 years. With respect to the frequency of injection, 24.7% of subjects injected one to three times a month; 35.5%, one to three times a week; and 39.8%, more than three times a week. We found a very high frequency of needle sharing (64.3%) during the six months prior to the interview (Table 1).

Participants possessed nearly high sexual risk behaviors. Despite sexual orientation (hetero- or homo-sexual) or the nature of the partnership (principal or occasional partners, or clients), a large proportion of participants reported irregular or no

Table 1. Association between HBV and HBV/ HDV infection with independent factors.

Variable		Patient Status		OR (95% CI)	P Value
		Single Infection (HBV)	Dual Infection (HBV & HDV)		
		Cases (%)	Cases (%)		
Sex	Male	17 (89)	5 (83)	1.7 (0.00-35.0)	NS*
	Female	2 (11)	1 (17)		
	Total	19 (100)	6 (100)		
Age group	<35	14 (74)	4 (67)	1.4 (0.13-14.57)	NS
	≥35	5 (26)	2 (33)		
	Total	19 (100)	6 (100)		
ART	Yes	0 (0)	1 (17)	0.0 (0.0-5.64)	0.24
	No	19 (100)	5 (83)		
	Total	19 (100)	6 (100)		
CD4	≤200	5 (26)	1 (17)	1.79 (0.13-50.90)	NS
	>200	14 (74)	5 (83)		
	Total	19 (100)	6 (100)		
HBeAg	+	15 (80)	0 (0)	-	0.001
	-	4 (20)	6 (100)		
	Total	19 (100)	6 (100)		
BMI	≥25	2 (11)	1 (17)	0.59 (0.03-20.40)	NS
	<25	17 (90)	5 (83)		
	Total	19 (100)	6 (100)		
IDU	Yes	19 (100)	5 (83)	-	0.24
	No	0 (0)	1 (17)		
	Total	19 (100)	6 (100)		
History of imprisonment	Yes	17 (90)	4 (67)	4.25 (0.29-68.37)	0.23
	No	2 (11)	2 (33)		
	Total	19 (100)	6 (100)		
Tattooing	Yes	18 (95)	5 (83)	3.60 (0.0-168.21)	NS
	No	1 (5)	1 (17)		
	Total	19 (100)	6 (100)		
History of unprotected sex	Yes	12 (63)	3 (50)	1.71 (0.19-15.65)	NS
	No	7 (37)	3 (50)		
	Total	19 (100)	6 (100)		
Cigarette smoking	Yes	19 (100)	5 (83)	-	NS
	No	0 (0)	1 (17)		
	Total	19 (100)	6 (100)		

* Not statistically significant

use of condoms (over 70% for all partnerships under analysis).

Of the 888 HIV-infected patients studied, 19 (2.13%) had only HBV co-infection, 35 (3.94%) had only HCV co-infection and 16 (1.80%) had multiple hepatitis viral infections of whom, five (25%) had dual hepatitis (four with B and C and one with B and D) and 15 (75%) had triple hepatitis (B, C, and D). Out of 15 patients with hepatitis B, C, and D, 10 had past/non-replicative hepatitis D (positive total anti-HD, and negative HD IgM) and five had chronic/replicative hepatitis D (repeatedly positive HD IgM). The serum of all of our HDV-infected subjects (n=15), with positive total anti-HDV antibodies, were negative for hepatitis D antigen.

Patients infected with multiple hepatitis viruses had acquired HIV through injecting illicit drugs (Table 1). Probably, patients infected only with HBV had acquired HIV infection through unprotected sex. When a comparison was made for patients infected with single and multiple hepatitis viruses, there were no statistically significant differences regarding demographics, CD4 cell count, and proportion of HIV-infected individuals receiving antiretroviral therapy. Patients with multiple hepatitis had a significantly ($P<0.001$) higher proportion of cirrhosis than those with hepatitis B (40%) or hepatitis C (9.7%). Among HCV-infected individuals, those with multiple hepatitis were significantly more likely to have a negative serum HCV RNA tested by reverse transcriptase polymerase chain reaction (RT-PCR). Among HBV-infected individuals, those with multiple hepatitis were significantly more likely to have a negative serum hepatitis B e antigen (HBeAg) and a positive antibody to hepatitis B e antigen (HBeAb). Tables 2 and 3 show other findings of our study.

Discussion

In a group of patients living with HIV/AIDS in the Kermanshah, we were able to find both common and unique epidemiological aspects of co-infection with HBV, HCV and HDV. To the best of our knowledge, this is the first study for estimating the prevalence of co-infection between HIV and HDV in the Islamic Republic of Iran. The study population comprised nearly all known registered and HIV-infected persons in the region. The prevalence rates for HIV and co-infection with hepatitis viruses found in this study were much lower than those reported elsewhere. Nearly low prevalence rates observed in our study was probably associated with the different local epidemiology of these viruses, and differences in the

Table 2. Association between HCV and HBV/ HCV infection with independent factors.

Variable		Patient Status		OR (95% CI)	P Value
		Single HCV infection	Dual Infection (HBV & HCV)		
		Cases (%)	Cases (%)		
Sex	Male	32 (91)	10 (100)	0.00 (0.00-8.75)	NS*
	Female	3 (9)	0 (0)		
	Total	35 (100)	10 (100)		
Age group	<35	20 (57)	7 (70)	0.57 (1.10-3.11)	NS
	≥35	15 (43)	3 (30)		
	Total	35 (100)	10 (100)		
ART	Yes	2 (6)	1 (10)	0.55 (0.03-17.16)	NS
	No	33 (94)	9 (90)		
	Total	35 (100)	10 (100)		
CD4	≤200	10 (29)	4 (40)	0.60 (0.11-3.26)	NS
	>200	25 (71)	6 (60)		
	Total	35 (100)	10 (100)		
HBeAg	+	0	7 (700)	-	
	-	0	3 (30)		
	Total	35 (100)	10 (100)		
BMI	≥25	9 (26)	4 (40)	0.40 (0.07-2.33)	NS
	<25	26 (74)	6 (60)		
	Total	35 (100)	10 (100)		
IDU	Yes	35 (100)	10 (100)	-	
	No	0 (0)	0 (0)		
	Total	35 (100)	10 (100)		
History of imprisonment	Yes	30 (86)	9 (90)	0.67 (0.03-7.57)	NS
	No	5 (14)	1 (10)		
	Total	35 (100)	10 (100)		
Tattooing	Yes	28 (80)	8 (80)	1.00 (0.12-7.16)	NS
	No	7 (20)	2 (20)		
	Total	35 (100)	10 (100)		
History of unprotected sex	Yes	20 (57)	7 (70)	0.57 (0.10-3.11)	NS
	No	15 (43)	3 (30)		
	Total	35 (100)	10 (100)		
Cigarette smoking	Yes	35 (100)	10 (100)	-	
	No	0 (0)	0 (0)		
	Total	35 (100)	10 (100)		

* Not statistically significant

degree of overlap of risk factors for infection with these viruses, which is believed to be the major determinant of co-infection with viral hepatitis among persons living with HIV/AIDS.

Our study had some limitations. For example, the study population represented only those we are taking care of. While our center includes the vast majority of HIV-infected individuals in Kermanshah receiving health care, hence, it does not include those who are not receiving medical care or unaware of their HIV infection. In spite of some potential limitations, our data signal important public health issues. Our data reveal an important national opportunity for the implementation and evaluation of blood-borne pathogens prevention programs among HIV/AIDS drug abusers through harm reduction strategies. Although universal childhood HBV vaccination was implemented 10 years ago, there still remains a large adult population at risk, for instance, persons living with HIV/AIDS. Establishment of specific strategies and programs is needed to reach these population at risk.

In our sample, the most frequently injected drug was heroin (92%). This seems to be an important aspect of the Iranian drug scene, since heroin injectors are under higher risk for blood-borne pathogen infections when compared with other drugs in our region. This is particularly for sharing needles and syringes. In our study population, we found that transition from non-injecting to injecting illicit drugs took a period from months to years, which highlights the need for establishing preventive programs directed at both injecting and non-injecting drug abusers for decreasing the likelihood of acquisition of blood-borne pathogens like HBV, HCV and HDV.

The fundamental approach to prevent HDV infection is to prevent infection with HBV. In this regard, proper immunization with hepatitis B vaccine will prevent infection with HDV provided that one is not already infected. The only way to prevent HDV infection for those already infected with HBV is to avoid contact with blood and serous fluids, to never share needles for drug use, ear piercing, tattooing or other means that increase the chance of blood-borne infections, and to use condoms when having sex. The use of hepatitis B immune globulin (HBIG), immune globulin (IG) or hepatitis B vaccine will not protect people against hepatitis D in those who are already have HBV infection [10]. In a recent study performed in Spain, serologic markers showed that more than 50% of HIV-infected patients with a positive serum HBs-Ag have been exposed to HDV [11]. This high prevalence of HDV infection in HIV-infected

Table 3. Association between HBV and HCV infection with independent factors.

Variable		Patient Status		OR (95% CI)	P Value
		Single Infection (HBV)	HCV		
		Cases (%)	Cases (%)		
Sex	Male	17 (89)	32 (91)	0.80 (0.09-7.68)	NS*
	Female	2 (11)	3 (9)		
	Total	19 (100)	35 (100)		
Age group	<35	14 (74)	20 (57)	2.10 (0.54-8.55)	NS
	≥35	5 (26)	15 (43)		
	Total	19 (100)	35 (100)		
ART	Yes	0 (0)	2 (6)	0.00 (0.00-7.87)	NS
	No	19 (100)	33 (94)		
	Total	19 (100)	35 (100)		
CD4	≤200	5 (26)	10 (29)	0.89 (0.21-3.67)	NS
	>200	14 (74)	25 (71)		
	Total	19 (100)	35 (100)		
HBeAg	+	15 (80)	0	-	
	-	4 (20)	0		
	Total	19 (100)	35 (100)		
BMI	≥25	2 (11)	9 (26)	0.44 (0.05-2.77)	NS
	<25	17 (90)	26 (74)		
	Total	19 (100)	35 (100)		
IDU	Yes	19 (100)	35 (100)	-	
	No	0 (0.0)	0 (0)		
	Total	19 (100)	35 (100)		
History of imprisonment	Yes	17 (90)	30 (86)	1.42 (0.21-11.95)	NS
	No	2 (11)	5 (14)		
	Total	19 (100)	35 (100)		
Tattooing	Yes	18 (95)	28 (80)	4.50 (0.47-105.63)	NS
	No	1 (5)	7 (20)		
	Total	19 (100)	35 (100)		
History of unprotected sex	Yes	12 (63)	20 (57)	1.29 (0.35-4.74)	NS
	No	7 (37)	15 (43)		
	Total	19 (100)	35 (100)		
Cigarette smoking	Yes	19 (100)	35 (100)	-	
	No	0 (0)	0 (0)		
	Total	19 (100)	35 (100)		

* Not statistically significant

patients with multiple hepatitis is somewhat unexpected. Although hepatitis D is endemic in the Mediterranean area, a number of reports have suggested a significant decrease over the past 20 years in the prevalence of hepatitis D in the general population [12]. One study performed in 1988 in Spain revealed a prevalence of 67% of positive serum hepatitis D markers among patients with hepatitis B and a history of injecting illicit drugs [13].

Although this prevalence is very different from the prevalence found in our study (0.67%), there is no doubt that HIV-infected IV drug abusers continue to be a reservoir of hepatitis D [14]. Because in our region IV drug abusers constitute an important source of blood-borne viral infections, they can play an important role in the transmission of viruses to the general population. Therefore, a public health intervention with implementation of comprehensive preventive strategies including information, face-to-face education, voluntary counseling and testing, empowerment programs, distribution or exchange of clean injecting equipments and distribution of condoms must be encouraged. These measures are especially relevant in developing countries like Iran, where public health programs are under-budgeted and under-staffed and frequently lack adequate infrastructures to implement these programs.

In our opinion, hepatitis B vaccination of all IDUs should be mandatory, not only as a direct strategy for prevention of new HBV infections, but also as a way to contact hard to reach IDUs and engage them in different preventive activities. Current vaccination strategies emphasize that this is a feasible and practical intervention, with a high cost/benefit ratio both in terms of human lives to be saved and financial resources to be spared.

Finally, we recommend sustained information and education of general population about the following strategies for decreasing acquisition of blood-borne viral pathogens like HDV:

- Not using illicit drugs
- Avoiding unsanitary tattooing
- Avoiding unsanitary body piercing
- Avoiding needle stick injury
- Avoiding sharing of grooming utensils
- Avoiding unprotected sex

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