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SEROLOGICAL MARKERS AND RISK FACTORS FOR HEPATITIS B AND C VIRUSES IN PATIENTS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS

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SUMMARY

Both hepatitis B and hepatitis C viruses (HBV and HCV) infection are common in HIV-infected individuals as a result of shared risk factors for acquisition. A serological study for HBV and HCV was performed in 251 HIV-positive individuals from Medellín, Colombia. A qualitative RT-PCR for HCV was done in 90 patients with CD4+ T-cell count ≤ 150 per mm^3. Serological markers for HBV infection were present in 97 (38.6%) patients. Thirty six of them (37.1%) had isolated anti-HBc. A multivariate analysis indicated that the following risk factors were significantly associated with the presence of these markers: age (OR = 1.05, 95% CI: 1.01-1.08), pediculosis pubis (OR = 1.83, 95% CI: 1.01-3.33), men who have sex with men and women (OR = 3.23, 95% CI: 1.46-7.13) and men who have sex only with men (OR = 3.73, 95% CI: 1.58-8.78). The same analysis restricted to women showed syphilis as the only significant risk factor. Thus, HBV infection was considerably associated with high risk sexual behavior. HCV was present in only two (0.8%) of HIV patients. Both of them were positive by RT-PCR and anti-HCV. This low frequency of HIV/HCV coinfection was probably due to the uncommon intravenous drug abuse in this population. The frequent finding of isolated anti-HBc warrants molecular approaches to rule out the presence of cryptic HBV infection.

KEYWORDS: Hepatitis B virus; Hepatitis C virus; Human immunodeficiency virus; Risk factors; Hepatitis C diagnosis; Serological markers.

INTRODUCTION

Hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) share certain epidemiological characteristics such as risk populations and transmission routes: parenteral, sexual and vertical. Consequently, HBV and HCV coinfection is a frequent event and increases in HIV positive persons. HIV/HCV can be found in eight to 30% of all HIV infected individuals[3,5,28,29,31,32,35], and approximately 50 - 92% of these are intravenous drug users. Similarly, evidence of past HBV infection can be as high as 50 - 80% of all HIV infected individuals[8,15,16,19]. This prevalence varies depending on the geographical area and the risk of the studied population[3,5,8,15,16,17,28,29,31,32,35].

HIV/HCV coinfection has a negative impact on the disease caused by HCV, accelerating its evolution. Some studies have associated HCV coinfection with a faster HIV progression, although this conection is controversial[5,18,21-23,30]. HCV infection also increases the toxicity to antiretroviral medications[9,18,26,27,32].

HIV/HBV coinfected patients have a higher risk of developing cirrhosis related to HBV, exhibit higher levels of HBV replication, lower rates of spontaneous resolution of the HBV infection, higher risk of reactivation of previous infections, and higher liver toxicity associated with antiretroviral therapy[8,10,15,19]. Whether or not, HBV coinfection alters the course of HIV progression has also been a matter of discussion[8,11,15,19,34].

In spite of widespread evidence of HBV/HIV and HCV/HIV coinfections, and the increasing prevalence of HIV, there are few reports[36] about the frequency of infections by these hepatitis viruses in HIV positive patients in Colombia. The objectives of this study were: i) to determine the frequency of serologic evidence of HBV and HCV infection in a group of HIV infected patients, ii) to explore risk factors associated with the presence of markers for these viruses, and iii) to compare the results obtained with serological and molecular biology tests for HCV diagnosis in patients with a low CD4+ T-cell count.

MATERIALS AND METHODS

Study population: A cross sectional study with a prospective selection of patients was carried out among HIV positive individuals consulting between October of 2002 and April of 2004 to the following health institutions in Medellín, Colombia: Hospital la María, Susalud

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EPS, Comfenalco EPS and Clínica Universitaria Bolivariana. Individuals that were ≥ 18 years old with current affiliation to the social security system, and a recent CD4+ T-cell count (during the last 4 - 6 months) were included. Two hundred and fifty one patients meeting these criteria agreed to participate in this non-random sample. A clear explanation of the objectives and implications of the results were given to each participant. Subsequently, an institution-approved informed consent was signed, and a clinical and epidemiological survey of risk factors was performed by personal interview. Twenty mL of peripheral blood were taken in EDTA and dried tubes; plasma and serum samples were aliquoted and stored at -70 °C until used.

Hepatitis B study: A screening test to detect antibodies to hepatitis B core antigen (anti-HBc) in serum was carried out by the microparticle assay, MEIA (Abbott Axsym® system, North Chicago, USA). Positive samples for this marker were further analyzed for the presence of hepatitis B surface antigen (HBsAg), immunoglobulin M to core antigen (IgM-HBc), and antibodies to hepatitis B surface antigen (anti-HBs) by MEIA (Abbott Axsym® system, North Chicago, USA). Based on the results, HBV infection was classified as: recent, immunolgical window, chronic, isolated anti-HBc, and resolved infection.

Hepatitis C study: A serological presumptive test for the detection of HCV antibodies (anti-HCV) was carried out by ELISA (Cobas/Core® Anti-HCV EIA II, Roche® Penzberg, Germany). Any positive result for anti-HCV was retested in duplicate by a second ELISA. A qualitative RT-PCR to detect HCV RNA in plasma (Amplicor® Hepatitis C Virus Test v2.0 Branchburg, USA) was carried out in patients with a double reactive presumptive test. Additionally, the qualitative RT-PCR was also carried out in the 90 patients with a CD4+ T-cell count ≤ 150 per mm^3 to determine diagnosis agreement with the two tests (ELISA and RT-PCR). This value was chosen based on previous reports indicating

Table 1
Clinical and epidemiological characteristics of 251 HIV positive patients

Characteristics	Total n = 251	According to gender	
		Male	Female
Sex, No. (%).	251	215 (85.6)	36 (14.3)
Age in years, X ± SD	37.9 ± 8.7	35.9 ± 8.4	38.3 ± 8.6
Age at beginning of sexual relation*, X ± SD	16.2 ± 3.3	16 ± 3.4	17.3 ± 2.7
Sexual workers,* No. (%)	11 (4.3)	6 (2.7)	5 (14.2)
Number of sexual partners†, Me (IQR)	18 (6-50)	20 (10-50)	3 (2-6)
Past history of STI*§, No. (%)	179 (71.6)	166 (77.2)	13 (37.1)
Sex with men and women*, No. (%)	101 (40.4)	100 (40)	1 (2.8)
Sex only with men*, No. (%)	95 (38)	61 (24.4)	34 (97.1)
Sex only with women*, No. (%)	54 (21.6)	54 (21.6)	0
Anal sex*, No. (%)		187 (74.8)	
CD4+ TL count X ± SD Range (min. - max.)		 298 ± 235 2-1569	
Condom use, No. (%) Never Sometimes Always		 108 (43.2) 137 (54.8) 5 (2)	
Drugs consumption, No. (%) Intravenous drugs, No. Needles or syringes exchange, No.		74 (29.5) 4 2	
Sexual partner user of IV drugs, No. (%)		9 (3.6)	
Tattoo, No. (%)		36 (14.3)	
Piercing, No. (%)		48 (19.1)	
Transfusion among 1982-1989‡, No. (%)		6 (2.3)	

* One transfusion-infected HIV female was excluded because absence of sexual intercourse;† Eleven sex workers and one transfusion-infected HIV female were excluded; ‡ Period of the time at which HIV screening in all the blood banks was not regulated; § Different from HIV and hepatitis sexual transmission.
STI = sexually transmitted infections; X = mean; SD = standard deviation; Me = median; IQR = inter quartile rank; IV = intravenous.

an increasing possibility of false negative results in tests for antibodies to HCV in coinfected patients with severe immunodepression[2].

Statical analysis: For data collection and analysis, Epi Info version 3.3.2 and SPSS version 10.0 (Chicago IL, USA) were used. Descriptive statistics are presented with mean and standard deviations (SD) or proportions, for continuous or categorical variables, respectively. Univariate and multivariate analyses of risk factors for serological markers of HBV infection were done for socio-demographic, clinical, epidemiological and laboratory variables through a logistic regression model. The results are presented as odds ratio (OR) with 95% confidence interval (95% CI). For other statistical significance tests, a two-tailed *p* value less than 0.05 was considered significant. The results of ELISA for anti-HCV and the qualitative RT-PCR for HCV RNA (gold standard) were compared in 90 patients with a CD4+ T-cell count ≤ 150 per mm^3 to evaluate agreement in the diagnosis.

RESULTS

Male gender predominance was observed (85.7%), and mean age was 37.9 (range 18 - 62 years). The main clinical and epidemiological characteristics of 251 HIV positive patients are presented in Table 1.

One hundred seventy nine patients (71.6%, n = 250 - one transfusion-infected HIV female was excluded due to the absence of sexual intercourse-) had a history of sexually transmitted infections (STI) different to HIV and hepatitis. These STI were more frequent in males (n = 166, 92.7%) than in females (n = 13, 7.2%, $p = 0.000001$). Most frequently reported STI were: urethritis 86 (34.4%), pubic pediculosis 84 (33.6%), condyloma 65 (26%), syphilis 43 (17.2%), herpes 31 (12.4%) and trichomoniasis 3 (1.2%). Almost half of the patients with such antecedent had had two or more different STI (n = 84, 46.9%).

HCV infection detected by anti-HCV occurred in only two patients (0.8%), both of them males, while the evidence of HBV exposure, detected by anti-HBc, was present in 97 (38.6%) of the patients. HCV RT-PCR was negative in all (89) patients with a low CD4+ cell count and non-reactive anti-HCV. It was positive only in the two anti-HCV reactive patients, which had 24 and 567 CD4+ cell per mm^3, respectively. Prevalence of anti-HBc antibodies was significantly higher in males compared to women (41.7% vs 22.2%, $p = 0.02$). More than half of anti-HBc positive patients had markers of resolved infection (anti-HBs positive and HBsAg negative). However, more than one third were anti-HBc positive and anti-HBs, IgM-HBc and HBsAg negative (Table 2).

In the univariate analysis, the following risk factors were significantly associated with serologic evidence of HBV infection: male gender, men who have sex only with men, men who have sex with men and women, a previous history of STI, a history of two or more STI, pediculosis pubis and syphilis (Table 3). In the multivariate analysis that included women and men the variables that were significantly associated were age, pediculosis pubis, syphilis, and type of sexual relation (Table 4). When the same model was fitted taking into account only males, the risk factors were age, pediculosis pubis, men who have sex only with men, and men who have sex with men and women (Table 5). The same analysis restricted to women showed syphilis as the only significant risk factor for the presence of serologic markers for HBV (OR: 26.0, CI 95%: 2.29-295.63, $p = 0.009$).

Table 2
Serological markers of HBV infection in 97 anti-HBc positive patients

Markers	No. (n = 97)	%	Interpretation
HBsAg (-), anti-HBs (+)	58	59.8	Resolved infection
HBsAg (-), anti-HBs (-), IgM-HBc (-)	36	37.1	Isolated anti-HBc
HBsAg (+), anti-HBs (-), IgM-HBc (-)	2	2.1	Chronic infection
HBsAg (+), IgM-HBc (+)	0	0.0	Recent infection*
HBsAg (-), anti-HBs (-), IgM-HBc (+)	1	1.0	Immunological window

* This pattern has occasionally been associated with chronic HBV infection.
Anti-HBc: antibodies to hepatitis core antigen; HBsAg: hepatitis B surface antigen; Anti-HBs: antibodies to hepatitis B surface antigen; IgM-HBc: immunoglobulin M to hepatitis B core antigen.

Table 3
Exploratory (univariate) analysis of the association of HBV markers with different risk factors

Independent variable	OR	CI 95%	*p* value
Male sex	2.47	1.02-6.20	0.02
Men who have sex only with men	3.54	1.43-8.89	0.002
Men who have sex with men and women	3.76	1.64-8.75	0.0005
Age at beginning of sexual relation before 16 years old	1.26	0.73-2.18	0.37
Past history of STI*	1.92	1.02-3.65	0.03
Past history of two o more different STI*	2.50	1.30-4.84	0.002
Type of STI:			
Urethritis	1	0.53-1.90	0.99
Condyloma	1.22	0.63-2.36	0.52
Pediculosis pubis	2.07	1.08-3.95	0.01
Herpes	1.52	0.65-3.54	0.28
Syphilis	2.90	1.35-6.28	0.002
CD4+ TL count ≤ 150 cells/mm^3 **	1.50	0.39-2.85	0.91

* Different from HIV and hepatitis of sexual transmission; ** This relation was explored for undetermined infection by HBV; STI: sexually transmitted infections.

DISCUSSION

The results of this study indicate that the frequency of HBV markers

Table 4
Unconditional logistic regression analysis of risk factors for HBV infection in 250 HIV positive patients*

Variables	OR	CI 95%	β Coefficient	Standard error	*Z*	*p*
Age**	1.04	1.004-1.073	1.073	0.017	2.189	0.029
Pediculosis pubis	1.96	1.099-3.492	3.492	0.295	2.280	0.023
Syphilis	2.59	1.259-5.315	5.315	0.367	2.587	0.001
Type of sexual relation 1/0†	2.86	1.285-6.263	6.263	0.408	2.575	0.010
Type of sexual relation 2/0†	2.21	0.978-5.024	5.024	0.418	1.906	0.056
Constant				0.741	-4.09	0.000

* One transfusion-infected HIV female was excluded due to the absence of sexual intercourse; ** Per year; † 0 = only women; 1 = men and women; 2 = only men.

Table 5
Unconditional logistic regression analysis of risk factors for HBV infection in 215 males with HIV

Variables	OR	CI 95%	β Coefficient	Standard error	*Z*	*p*
Age*	1.051	1.014-1.089	0.0497	0.018	2.757	0.006
Pediculosis	1.834	1.010-3.335	0.6067	0.305	1.990	0.047
Type of sexual relation 1/0†	3.236	1.469-7.130	1.1743	0.403	2.913	0.004
Type of sexual relation 2/0†	3.733	1.586-8.784	1.3171	0.437	3.016	0.003
Constant			-3.4536	0.786	-4.39	0.000

* Per year; † 0 = only women; 1 = men and women; 2 = only men.

(38.6%) is similar to that found in other Latin American countries[6,13,20]. In contrast, the frequency of anti-HCV in HIV patients (0.8%) is much lower than that found in previous reports from Brazil (Santos and São Paulo), Cuba and Argentina, where the seroprevalence of anti-HCV was 36.2%, 17.7%, 15.5%, and 58.5%, respectively[6,7,13,25]. The low frequency found in our study could be explained by the low incidence of intravenous drug use and the infrequent transfusions in this population, which are very different to those reported in the studies cited from Latin America where intravenous drug use[13,18,25] and past history of transfusion[7] were the main risk factors identified for HCV infection in HIV patients.

It is unlikely that the low seroprevalence of HIV/HCV coinfection was due to selection bias because subject in this study were selected from health institutions that covers a wide range of socio economic strata. Intravenous drug use has also rarely been associated with HIV infection in Colombia[14]; of 40,072 HIV infections reported in Colombia by 2002, 96.0% percent were likely transmitted by sexual intercourse, 3.1% were perinatally acquired, 0.67% transfusion related, and only 0.12% transmitted by other routes. It is estimated that about 0.4% of Colombian population is infected by HIV with a 3:1 male to female ratio[12].

The two individuals coinfected with HIV/HCV did not have a past history of transfusions, use of intravenous drugs, tattoos, piercing or sexual relations with a partner who was an intravenous drug user. However, they presented high risk sexual behaviors and past history of STI, suggesting that sexual intercourse could have been the route of viral infection. One of these was negative for anti-HBc and the other one had isolated anti-HBc (HBsAg, IgM-HBc, and anti-HBs negative). The CD4+ T-cell counts were 24 and 567 per mm^3, respectively. Both patients had active hepatitis C infection demonstrated by a positive qualitative RT-PCR. In contrast to false negative results previously reported for HCV serological tests in patients with very low CD4+ T-cell counts[2,4], the patient with 24 cells per mm^3 was doubly reactive with a maximum optical density (3.5) in the ELISA test, indicating that humoral immune responses were still present despite the low number of circulating CD4+ T-cells.

The frequency of HBV infection in our group of HIV patients was 38.6% which does not differ significantly from a previous report studying similar patients, in which the authors found that 45.7% of AIDS patients (43/94) were positive for HBV serological markers[36]. In the multivariate analysis, the risk factors associated with HBV markers were age, pediculosis pubis, syphilis, and type of sexual relation (Table 4). Among males the main risk factors associated were men who have sex only with men, men who have sex with men and women, pediculosis pubis and age (Table 5). In women, syphilis was the main risk factor associated with HBV infection. These data suggest that sexual intercourse is the most probable route hepatitis B exposure regardless of the fact that HBV was not considered as a STI by the subjects of this study (data not shown). In groups of HIV positive patients from Argentina, Brazil and Cuba, the frequencies of HBV markers were 58.5%, 38.6%, and 45.5%, respectively[6,13,20]. In these studies the most important risk factors were male sex, intravenous drug use and/or high risk sexual behaviors.

Thirty six of 97 (37.1%) individuals with serological evidence of HBV infection had an isolated anti-HBc pattern. This finding is frequently observed in HIV positive patients, intravenous drug users and people infected by HCV[17,24]. The inability to detect HBsAg or anti-HBs in individuals positive for anti-HBc can be attributed to different factors such as low level of HBV replication, HBV genotype variations and mutations in pre-S/S genomic region, which can affect HBsAg detection by conventional techniques[1,24].

In summary, in this group of HIV positive patients, we found a frequency of HBV markers similar to that found in other Latin America countries. This was significantly associated with high-risk sexual behavior. In contrast, HCV coinfection was present in only two (0.8%) of HIV patients, a finding probably related to the uncommon use of intravenous drugs.

RESUMEN

Marcadores serológicos y factores de riesgo para los virus de la hepatitis B y C en individuos infectados por el VIH

La infección por los virus de la hepatitis B y hepatitis C (VHB y VHC) es frecuente en individuos infectados por el VIH como resultado de compartir factores de riesgo para su contagio. Se realizó un estudio serológico para el VHB y VHC en 251 individuos VIH positivos de la ciudad de Medellín, Colombia. En 90 pacientes con un recuento de linfocitos T ≤ 150 células por mm^3 se hizo una PCR-RT cualitativa para el VHC. Se encontraron marcadores serológicos para la infección por el VHB en 97 (38.6%) pacientes. Treinta y seis de 97 (37.1%) tuvieron un anti-HBc aislado. El análisis multivariado indicó que los factores de riesgo significativos asociados a la presencia de estos marcadores fueron: edad (OR = 1.05, 95% IC: 1.01-1.08), pediculosis púbica (OR = 1.83, 95% IC: 1.01-3.33), hombres que tienen sexo con hombres y mujeres (OR = 3.23, 95% IC: 1.46-7.13) y hombres que tienen sexo solo con hombres (OR = 3.73, 95% IC: 1.58-8.78). El mismo análisis restringido a mujeres mostró que la sífilis fue el único factor de riesgo significativo. Por lo tanto, la infección por el VHB fue considerablemente asociada a conductas sexuales de alto riesgo. El VHC se presentó en solo 2 (0.8%) de los pacientes VIH. Ambos pacientes fueron positivos por la PCR-RT y los anti-VHC. La baja frecuencia de la coinfección VIH/VHC fue probablemente debido al bajo uso de drogas intravenosas en esta población. El hallazgo frecuente de anti-HBc como marcador aislado asegura estudios moleculares para descartar la presencia de infección críptica por el VHB.

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