HTLV-I/II and blood donors: determinants associated with seropositivity in a low risk population

HTLV-I/II e doadores de sangue: determinantes associados à soropositividade em população de baixo risco

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Abstract

Objective
Blood donors in Brazil have been routinely screened for HTLV-I/II since 1993. A study was performed to estimate the prevalence of HTLV-I/II infection in a low risk population and to better understand determinants associated with seropositivity.
Methods
HTLV-I/II seropositive (n=135), indeterminate (n=167) and seronegative blood donors (n=116) were enrolled in an open prevalence prospective cohort study. A cross-sectional epidemiological study of positive, indeterminate and seronegative HTLV-I/II subjects was conducted to assess behavioral and environmental risk factors for seropositivity. HTLV-I/II serological status was confirmed using enzyme-linked immunosorbent assay (EIA) and Western blot (WB).
Results
The three groups were not homogeneous. HTLV-I/II seropositivity was associated to past blood transfusion and years of schooling, a marker of socioeconomic status, and use of non-intravenous illegal drugs.
Conclusions
The study results reinforce the importance of continuous monitoring and improvement of blood donor selection process.

Resumo

Objetivo
Doadores de sangue no Brasil têm sido avaliados sorologicamente para o HTLV-I/II desde 1993. Assim, realizou-se estudo para estimar a prevalência dessa infecção em população de baixo risco e para melhor compreender os determinantes associados à soropositividade.
Métodos
Doadores de sangue soropositivos (n=135), soroindeterminados (n=167) e soronegativos (n=116) foram arrolados como participantes de uma coorte aberta e prevalente. Estudo transversal dos participantes desses três grupos avaliou fatores

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de risco comportamentais e ambientais para soropositividade. O status sorológico foi definido usando a reação de EIA (enzyme linked immunosorbent assay) e o teste Western blot (WB).

Resultados

Os três grupos apresentaram heterogeneidade entre si. A soropositividade mostrou-se associada à história pregressa de transfusão de sangue, em nível educacional, como um marcador de condição socioeconômica e ao uso de drogas ilegais não endovenosas.

Conclusões

Os resultados confirmam a importância de um monitoramento e refinamento do processo de seleção dos doadores de sangue.

INTRODUCTION

Human lymphotropic viruses types I and II (HTLV I/II) were the first reported human retroviruses, having been isolated in the beginning of the 80's (Poiez et al [13]). In regions considered endemic (Caribbean, Africa and Southwest Japan), HTLV-I antibody prevalence range from 3% to 15%, it is higher in older individuals and in females (Blattner et al;[1] Chavance et al;[3] Tokudome et al[15]). Although it shares 65% of its genome with type I, HTLV-II is much less prevalent, predominating in native populations of the American continent and among injecting drug users in the United States and Europe (Hall et al[5]). The virus is transmitted vertically, especially through breastfeeding (Hirata et al[6]), sexually (Kajiyama et al[8]), and with the exposure to infected blood, mostly through blood transfusions or syringes and needles sharing among intravenous drug users (Sullivan et al,[14] Okochi et al[12]).

HTLV-I/II serological screening has become mandatory in Brazilian blood banks since November 1993. Among the 405,437 volunteers donating blood at Hemominas Blood Center, between January 1994 to January 1999, 3,203 (0.79%) were EIA positive. For those 405,437 blood donors, 244 (0.06%) were confirmed as positive in the Western Blot test and 1,454 (0.36%) were considered indeterminate.

An open prevalence prospective cohort study (The Interdisciplinary HTLV-I/II Research Group [GIPH] Cohort Study) is being conducted at the Hemominas Blood Center since March 1997. In an attempt to better understand the epidemiological aspects of the virus seroprevalence, and to define the infection's determinants in this population, as well as to subsidize the screening criteria in local blood banks, a case-control study with cross-sectional features of the social-economic, demographic and behavior variables at baseline of the GIPH Cohort Study participants was conducted.

METHODS

Hemominas Institute is located in the metropolitan area of Belo Horizonte , state of Minas Gerais, Southeast Brazil. Belo Horizonte has about 4,000,000 inhabitants and it is the third largest city in Brazil. Hemominas Institute, the blood bank of the state of Minas Gerais, is the largest blood bank in the city. In 2000 an average of 7,000 individuals/month donated blood at Hemominas and 15,000 blood transfusions/month were made. After a routine pre-donation screening questionnaire and clinical examination, individuals who are considered eligible for blood donation - aged between 18 and 60 years, good general health, not being exposed to retrovirus risk factors (for example, use of illegal injecting drugs, unsafe sexual behavior, tattoos), and not having received blood or blood products transfusions in the last 10 years - are tested for blood transmitted infections, namely HIV-1/2, HBV, HCV, *T. cruzi, T. pallidum* and HTLV-I/II. Blood donors in Brazil are all volunteers because any reimbursement for blood donation is prohibited by law.

For HTLV-I/II, an eligible donor is considered positive when their enzymatic serological testing (ELISA) is reactive, and the confirmatory testing, Western Blot (WB), also shows positive results according to the manufacturer's instructions: there is a band at p24 and gp46 or p21env (1998); reactivity to GAG (p19 and p24) and ENV (GD21) - (1998 to 2000). A reactive EIA and the presence of any band pattern different from manufacturer's criteria for positivity is classified as indeterminate. Individuals whose EIA test was not reactive are considered seronegative; also, those whose EIA test was not reactive and there were no bands in the Western Blot are considered seronegative.

Any former blood donor of the Hemominas Institute living in the metropolitan area of Belo Horizonte with HTLV-I/II positive or indeterminate results since the

start of the GIPH Cohort Study were eligible to the study. A sample of seronegative donors (n=348) selected using a systematic random sampling, who donated blood during the same period of time in the same network, was included in the study. Subjects with abnormal serology, as well as the seronegative group, were contacted by mail and invited to an initial interview. After informed and counseled about their serological status, the study objective and procedures, an informed consent was obtained from those willing to participate. Data collected during the baseline visit of study participants' were analyzed and results are presented here.

All subjects answered the same questionnaire to the same interviewer in a private environment. The interviewer, who is one of the authors (BCS), was aware of participants' serological results. The interviews were conducted from March 1997 to June 1999.

The questionnaire was designed to elicit data on (a) demographics such as education level, personal monthly income, and occupation; (b) HTLV-I/II transmission: breastfeeding, blood transfusion at any time in the past, intravenous injection of illegal drugs, syringe and needle sharing, accidents involving another person's blood, tattoos, and acupuncture treatment. Questions about use of any recreational illegal drug and; (c) sexual history: number of partners, paid sex and male homosexual contacts were also asked. For women, information about reproductive history was also obtained.

To guide the interpretation, crude and stratified prevalence rates were calculated along with prevalence odds ratio and 95% confidence interval. Since all the variables were categorical, the answers were compared within the groups (positive, indeterminate and negative) using cross tabulation. The differences were tested for significance using the X^2 test or, when indicated, Fisher's exact test. Multinomial logistical regression models were also fitted to the data to better compare the three groups simultaneously (Hosmer & Lemeshow[7]). The variables shown to be statistically significant in the bivariate analysis were added to the logistical model (forward selection), and maintained in the final model if p<0.05 or if presenting biological plausibility to justify their remaining in the model, despite the p-value. Data analysis was conducted using Stata 6.0.

The Hemominas Institutional Board approved the study procedures.

RESULTS

During the study period, of all seropositive subjects (n=180) invited to participate in the GIPH Cohort Study, 75.0% (n=135) signed a consent as compared to about 33.0% of the indeterminate (n=506) and negative (n=348) groups. No significant difference in behavior and demographic variables distribution was found when comparing responding and non-responding subjects as a group or according to serologic results (data not shown).

The average subject age was 33 years, and 66.8%

Table 1 - Frequency distribution of HTLV-I/II serostatus according to demographic and behavior characteristics at baseline. The GIPH Cohort Study. Belo Horizonte, Brazil, 1997-1999.

Variables	HTLV-I/II positive (N=135) N (%)		HTLV-I/II indeterminate (N=167) N (%)		HTLV-I/II negative (N=116) N (%)	
	Men 74 (100.0)	Women 61 (100.0)	Men 126 (100.00)	Women 41 (100.0)	Men 75 (100.0)	Women 41 (100.0)
Age (years)						
18-29	23 (31.1)	16 (26.2)	58 (46.0)	17 (41.5)	44 (58.7)	21 (51.2)
30-39	25 (33.8)	18 (29.5)	46 (36.5)	9 (22.0)	20 (26.7)	13 (31.7)
40-49	20 (27.0)	17 (27.8)	18 (14.3)	10 (24.4)	8 (10.6)	5 (12.2)
50-60	6 (8.1)	10 (16.5)	4 (3.2)	5 (12.1)	3 (4.0)	2 (4.9)
Formal education						
≥8 years	12 (16.2)	16 (28.1)	42 (33.3)	18 (43.9)	38 (50.7)	26 (63.4)
<8 years	62 (83.8)	41 (71.9)	84 (66.7)	23 (56.1)	37 (49.3)	15 (36.6)
NA*		4				
Blood transfusion						
No	60 (83.3)	45 (86.5)	115 (93.5)	34 (89.5)	74(100.0)	39 (95.1)
Yes	12 (16.7)	7 (13.5)	8 (6.5)	4 (10.5)	0 (0. 0)	2 (4.9)
NA*	2	9	3	3	1	
Breastfed						
No	2 (2.7)	2 (3.6)	1 (0.8)	1 (2.7)	2 (2.9)	5 (12.5)
Yes	72 (97.3)	54 (96.4)	115 (99.2)	36 (87.3)	68 (97.1)	35 (87.5)
NA*		5	10	4	5	1
Non-intravenous Illegal drugs						
No	65 (87.8)	50 (87.8)	110(87.3)	32 (80.0)	71 (94.7)	39 (97.5)
Yes	9 (12.2)	7 (12.2)	16 (12.7)	8 (20.0)	4 (5.3)	1 (2.5)
NA*		4		1		1

*NA: Information not available.

were males. HTLV-I/II prevalence was higher in women (41.0%) than men (28.0%) (Table 1).

In the bivariate analysis (Table 2), when compared to seronegative donors, HTLV-I/II seropositive subjects were more often older, had fewer years of schooling, used non-intravenous recreational illegal drugs (marijuana as almost the single drug used), had blood transfusions in the past and paid for sex (males only). The indeterminate subjects when compared to seronegative donors (Table 3) were more likely to have fewer years of schooling, breastfeeding, use of non-intravenous recreational illegal drugs, blood transfusions in the past and paid sex (males only). No significant difference between the groups was found for the frequency distribution of tattoos, acupuncture and intravenous drugs use (data no shown).

The multinomial logistical regression model was applied to the group as a whole (Table 4). The final model comparing positive and indeterminate subjects to the negative group identified three main variables after adjusting for age and sex: history of previous transfusions, less than eight years of schooling, and use of non-intravenous recreational illegal drugs in the past. In Brazil schooling years is a well-recognized and accurate surrogate of socio-economic status. As education and monthly income are strongly correlated, only the variable education was included in the study models. For this study, education was assumed to be a measurement with higher accuracy and reliability than income.

DISCUSSION

The study results revealed remarkable lack of homogeneity between the three studied groups. This is very important when considering that all study subjects had self-assessed themselves as healthy enough to volunteer for blood donation. Also, all subjects were clinically asymptomatic when submitted to the routine pre-donation screening questionnaire and clinical examination conducted at Hemominas Institute. For the seropositive group it was observed an growing trend in the OR with increasing in the study population age (Table 4). The greater 95% confidence intervals may have resulted from small numbers especially for the 50-59 age group. Several different hypothesis can be formulated: the higher antibody titers in subjects infected for longer periods of time, the continuous addition of new infected individuals and the cohort effect, with older groups reflecting the highest infection prevalence rate in the past (Yamaguchi,[16] Murphy et al[11]).

From 1994 to 1998, women represented 22.9% (93,940/405,437) of the Hemominas Institute donors, and 42.2% (57/135) of the HTLV-I/II seropositive subjects. The higher seroprevalence in women than men points out to a higher effectiveness in transmission

Table 2 - Bivariate analysis for HTLV-I/II serologic status according to selected determinants at baseline: seropositive versus seronegative groups. The GIPH Cohort Study. Belo Horizonte, Brazil, 1997-1999.

Variables	HTLV-I/II positive N=135 N (%)	HTLV-I/II negative N=116 N (%)	OR	95% CI*
Sex				
Male	78 (57.8)	75 (64.7)	1.00	
Female	57 (42.2)	41 (35.3)	1.34	(0.78-2.30)
Age (years)				
18 to 29	39 (28.9)	65 (56.0)	1.00	
30 to 39	43 (31.9)	33 (28.5)	2.17	(1.14-4.16)
40 to 49	37 (27.3)	13 (11.2)	4.74	(2.12-10.75)
50 to 59	16 (11.9)	5 (4.3)	5.33	(1.66-18.23)
Formal education				
≥8 years	28 (20.7)	64 (55.2)	1.00	
<8 years	107 (79.3)	52 (44.8)	4.70	(2.61-8.52)
Breastfed				
No	4 (3.0)	7 (6.4)	1.00	
Yes	126 (97.0)	102 (93.6)	2.16	(0.53-10.32)
NA	5	7		
Non-intravenous Illegal drugs				
No	117 (86.7)	110 (95.7)	1.00	
Yes	18 (13.3)	5 (4.3)	3.38	(1.15-10.82)
NA		1		
Blood transfusion				
No	105 (84.7)	113 (98.3)	1.00	
Yes	19 (15.3)	2 (1.7)	10.22	(2.22-65.16)
NA	11	1		
Paid sex**				
No	40 (53.3)	48 (71.6)	1.00	
Yes	35 (46.7)	19 (28.4)	1.43	(1.04-4.73)
NA	3	8		

*Odds ratio and 95% Confidence Interval.
**For males only.

Table 3 - Bivariate analysis for HTLV-I/II serologic status according to selected determinants at baseline: indeterminate group versus negative group. The GIPH Cohort Study. Belo Horizonte, Brazil, 1997-1999.

Variables	HTLV-I/II indeterminate N=166 N (%)	HTLV-I/II negative N=116 N (%)	OR	95% CI*
Sex				
Male	126 (75.9)	75 (64.7)	1.00	
Female	40 (24.1)	41 (35.3)	0.57	(0.33-0.98)
Age (years)				
18 to 29	74 (44.6)	65 (56.0)	1.00	
30 to 39	55 (33.1)	33 (28.5)	1.44	(0.81-2.58)
40 to 49	28 (16.8)	13 (11.2)	1.87	(0.84-4.17)
50 to 59	9 (5.4)	5 (4.3)	1.56	(0.45-5.68)
Formal education				
≥8 years	60 (36.1)	64 (55.2)	1.00	
<8 years	106 (63.9)	52 (44.8)	2.19	(1.32-3.67)
Breastfed				
No	2 (1.3)	7 (6.4)	1.00	
Yes	152 (98.7)	102 (93.6)	5.22	(0.97-37.1)
NA	12	7		
Non-intravenous Illegal drugs				
No	143 (86.1)	110 (95.7)	1.00	
Yes	23 (13.9)	5 (4.3)	3.54	(1.22-10.99)
NA		1		
Blood transfusion				
No	149 (92.5)	113 (98.3)	1.00	
Yes	12 (7.5)	2 (1.7)	4.55	(0.94-30,06)
NA	5	1		
Paid sex**				
No	58 (48.3)	48 (71.6)	1.00	
Yes	62 (51.7)	19 (28.4)	2.70	(1.36-5.40)
NA	6	8		

*Odds ratio and 95% Confidence Interval.
**For males only.

from men to women, and/or to hormonal factors and possibly other unknown determinants and exposures. All these findings corroborate previous reports (Manns & Blattner,[10] Clark[4]) where the interplay of two or more determinants was suggested (Kajiyama et al,[8] Clark et al,[4] Brodine et al[2]). However, in the final logistic regression model, after adjusting for age, previous history of transfusion, years of schooling and use of illegal non-intravenous drugs, it was found that HTLV-I/II serological status was independent of participants' sex. It is possible that in the study population, sex may be a marker of social inequality and/or a confounder of the association of HTLV-I/II serology and education - a marker for socio-economic status.

The results of the indeterminate group should be considered bearing in mind that this group has subjects with false positive results (cross-reaction? malaria? dengue? other retroviruses?) who could be infected with different virus strains (Chavance et al,[3] Kaplan et al[9]) as well as the individuals actually infected with HTLV-I/II without a full-blown

Table 4 - Multinomial logistic regression of HTLV-I/II serological status according to selected variables, at baseline. GIPH Cohort Study. Belo Horizonte, 1997-1999.

Variables	HTLV-I/II positive*		HTLV-I/II indeterminate*	95% CI
Sex				
Male	1.00**		1.00**	
Female	0.72	0.40-1.28	1.64	0.95-2.84
Age				
18-29	1.00		1.00	
30-39	1.61	0.83-3.11	1.24	0.70-2.22
40-49	3.76	1.69-8.34	1.74	0.81-3.73
50-59	2.53	0.78-8.14	1.17	0.36-3.84
Transfusion				
No	1.00		1.00	
Yes	10.02	2.17-46.33	4.84	1.04-22.96
Formal education				
>8 years	1.00		1.00	
≤8 years	4.06	2.21-7.45	1.97	1.78-3.29
Non-intravenous Illegal drugs				
No	1.00		1.00	
Yes	3.25	1.08-9.73	3.57	1.28-9.92

*HTLV-I/II negative is the comparison group.
**Odds ratio and 95% Confidence Interval.

serological response detectable in the Western blot.

The present results clearly show that the indeterminate group is different from the seropositive and seronegative groups, presenting demographics and behavior characteristics (e. g., sex, age, breastfeeding) similar to the negative group, but matching the positive group in terms of past history of blood transfusions, less than eight years of schooling and use of recreational non-intravenous drugs (Tables 2, 3 and 4). Eleven percent of the indeterminate subjects had positive polymerase chain reaction (PCR). Of these, some have shown overt seroconversion at the time of the biannual reevaluation (manuscript in preparation). To one's knowledge, not much has been investigated about the epidemiological characteristics of the indeterminate group, which makes it difficult to compare the study data with the literature.

The present study has allowed the evaluation of various demographics, socio-economic and behavior characteristics associated to HTLV-I/II infection, and contrasts between positive and indeterminate serology groups. Some new determinants associated with HTLV-I/II seropositivity were identified, such as non-intravenous use of recreational illegal drug use, especially marijuana, and low socioeconomic conditions, measured by years of schooling, both of them relatively valid markers for income and social status. These data point out toward significant inequalities as determinants of exposure to HTLV-I/II infection. The study population, where well-known determinants of HTLV-I/II infection were by definition exclusion criteria of study participation, make possible to show inequalities of the study population as a determinant of HTLV-I/II seroprevalence. Although lower education has been associated with higher risk of other blood-borne virus infections, such as HIV and Hepatitis B and C (Goubau*), it has not been conclusively associated with HTLV infection.

Some study limitations should be also considered. For example, blood donors are not representative of the base population in age and sex distribution and may be also healthier, a possible "healthy blood donor effect". Concerning HTLV-I/II distribution in the base population, seropositive blood donors are more likely to include younger asymptomatic males individuals who were more recently infected. Although most of HTLV-I/II seropositive individuals are apparently asymptomatic through out their lives, the study cross-sectional data analysis may have resulted in an undetected survival bias. Also, as for all individuals donating blood in a public health blood center, participants were informed of their serologic results before being invited to join the study. As a consequence, neither participants nor the interviewer were blind as for participants' serological status. Although only one experienced and well-trained interviewer conducted all interviews, interviewer bias may not be ruled out. The advantages of this population are that blood donors' status is more easily and less expensively ascertained as compared to a random sample of the base population, and these individuals are also a healthier non-institutionalized population.

The strong association between blood transfusions in the past year and uncertainties concerning chronic infection, as well as the actual significance of indeterminate results call for a careful approach regarding counseling and follow-up protocols.

In this manner, it will be possible to elaborate public health measures to minimize the risk of asymptomatic HTLV infected individuals developing HTLV-I/II-related diseases, and to control virus transmission. It is believed that the study's findings may be valuable in the reevaluation of criteria for blood donor selection, further understanding of virus infection spread and prevention, and reinforcing the need of a more in depth assessment of the indeterminate serology group.

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