

HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE I (HTLV-I) SEROEPIDEMIOLOGY AND RISK FACTORS IN METROPOLITAN PANAMÁ

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Human T-cell lymphotropic virus type I (HTLV-I) infection and associated hematologic malignancies cluster in Japan, the Caribbean basin, and Central Africa. The authors believe that this study of HTLV-I seroepidemiology in the Republic of Panamá is the first detailed analytic study of environmental factors pertaining to HTLV-I infection in representative tropical populations. The study analyzed observational data concerning housing conditions, family composition, and demographic and behavioral attributes as risk factors for HTLV-I infection (HTLV-I antibody). The 745 study subjects were residents of representative households in Panamá City and Colón. Overall, 5% of sera had antibody against HTLV-I, detected by enzyme-linked immunosorbent assay and confirmed by competitive binding. Housing conditions, race, and socioeconomic factors were not associated with infection nor did infection cluster in families. Interview of 706 women enrolled in cervical cancer studies documented that female sexual experience (number of marriages or sexual partners) was associated with HTLV-I infection. These findings support the hypothesis that HTLV-I is not transmitted by casual contact but requires exposures involving exchange of bodily fluids.

human T-cell leukemia virus; retrovirus infections; serology; virus diseases

Human T-cell lymphotropic virus type I (HTLV-I) is an exogenous human retrovirus which specifically infects helper T-lymphocytes (OKT4⁺) and causes adult T-cell leukemia/lymphoma (1). Most HTLV-I isolates from throughout the world have been closely related, as determined

by serology and molecular hybridization (2, 3). HTLV-I infection and adult T-cell lymphoma cluster in Japan, the Caribbean basin, and parts of Africa (4).

The most detailed studies of HTLV-I and adult T-cell lymphoma have been conducted in Japan, where infection and dis-

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Abbreviations: ELISA, enzyme-linked immunosorbent assay; HTLV-I, human T-cell lymphotropic virus type I.

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ease cluster on the southern islands (5). People born in the rural, more tropical coastal areas of Japan are at excess risk for HTLV-I infection and adult T-cell lymphoma regardless of current residence (6). Preliminary reports from Japan have indicated that infection may cluster in families, and it has been suggested that both husband-to-wife transmission and mother-to-child transmission occur (7). Similar but less complete studies have shown that HTLV-I and associated myeloproliferative malignancies are common among blacks from the Caribbean basin (8, 9). The ethnic and racial composition is different from that which exists in Japan, but the geographic setting is in many ways comparable. None of these studies have analyzed detailed environmental-epidemiologic risk factors for HTLV-I infection in defined normal populations.

The Republic of Panamá presents a unique setting in which to study the epidemiology of HTLV-I and adult T-cell lymphoma. Panamá is a tropical Caribbean basin country with a stable population composed of several distinct, racial/ethnic groups; a large black population of West Indian descent resides in Panamá City, Colón, and Caribbean coastal towns. The current analysis presents studies of HTLV-I infection in Panamá City and Colón and is the first cross-sectional study of HTLV-I in which sera and detailed epidemiologic data have been collected from defined, normal Latin American populations.

MATERIALS AND METHODS

Study populations

We used sera and descriptive data collected during two recent Gorgas Memorial Laboratory cross-sectional studies of de-

defined populations. These populations are best characterized geographically.

Panamá City. Panamá City (population 610,384), the Pacific terminus of the Panamá Canal, is the capital of Panamá, and approximately 33 per cent of the Republic's population reside in the city. Immigration is intense, and, in some boroughs, population densities exceed 3,000 people per km². A survey intended to represent the general population of Panamá City was conducted in 1981 during an echo 4 virus aseptic meningitis epidemic (10). The epidemic involved the entire city and encompassed 1,032 hospitalized pediatric cases. Case families were defined by a random 10 per cent selection of diagnosed aseptic meningitis patients. Survey teams contacted an adult head of household, explained the purpose of the study, and solicited the family's cooperation. If no one was home, up to three return visits were made. If a family could not be contacted, or verbal, informed consent was not given, the case was not replaced.

For each case family, a neighboring control family was selected (10). This was the closest residence to the case home with at least one child younger than 15 years of age, and in which no one had been diagnosed with aseptic meningitis. For every two case families in a borough, a distant control family was selected to be representative of the borough. When a potential control family was located, the same procedures were utilized as with case families, except that, if permission was refused, the next closest eligible neighboring family was substituted.

Data collection involved inspection of the residence and recording observations on a standardized form which included address, type of house, number of rooms, number of residents, number of people per sleeping room, water source, and sanitary facilities. Standardized interviews were conducted to document monthly household income and family pets, and each resident's age, sex, race, and occupation. Finally, 10 ml of blood was collected from willing res-

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idents older than age one year (83 per cent of the study population permitted phlebotomy).

Colón. Colón (population 60,000) is the second largest city in Panamá and occupies a peninsula in Limon Bay, the Panamá Canal Caribbean anchorage. Blacks of West Indian ancestry comprise a large proportion of Colón's population. A representative sample of Colón was obtained in 1981 during a study of enterovirus type 70 acute hemorrhagic conjunctivitis (11). Study teams covered two block-wide transects of the city and surveyed one household per block (11). If a residence was unoccupied, the head of household could not be found, or the family refused to participate, the next closest household was selected. If a responsible adult was not present, the team attempted to ascertain his (her) whereabouts and to locate him (her), and verbal informed consent was solicited. Fewer than 1 per cent of families refused to participate. Household and interview data and sera were obtained as in the meningitis study.

Special female populations

This report also includes data from two cervical cancer studies which collected serum and information on sexual and other cancer risk factors. The first study involved 444 women enrolled during a cervical cancer case-control study in Herrera Province and the second included 262 female employees of the National Lottery in Panamá City.

Herrera Province. The study in Herrera Province was conducted in 1980 and included all female residents of the Province who were diagnosed with in situ or invasive cervical cancer during 1974-1980 (12). Controls were identified by asking cases to provide names of four women within five years of their own age who had resided in the same neighborhood at the time of diagnosis. Interviews were almost always obtained with the closest two neighbors or, in the rare instance when they were unavailable, from the remaining potential controls.

National Lottery, Panamá City. The National Lottery is a government-operated business which employs approximately 600 women at its Panamá City headquarters. In 1980, we obtained interviews and blood specimens from 262 female employees who volunteered to participate in a woman's health survey; the objective was to test interview methods for the cervical cancer case-control study.

Laboratory methods

Blood specimens were collected by venipuncture using 10 ml vacutainer systems. Blood was allowed to clot at ambient temperature and was then held on wet ice for 2-12 hours until processed. Serum was removed, aliquoted into small volumes, and stored at -20 C until tested for HTLV-I antibody.

All serum samples were screened for HTLV-I antibody by the enzyme-linked immunosorbent assay (ELISA) technique, using HTLV-I whole virus antigen that was zonal ultracentrifugation purified and detergent disrupted (13). Sera with binding ratios in excess of two times that of a standard negative control serum were retested in a confirmation assay. Confirmation was by competition with heterologous HTLV-I antiserum containing no detectable reactivity against phytohemagglutinin stimulated normal human lymphocytes. Results were considered confirmed when the competition was greater than 50 per cent of the uncompleted sera (14).

RESULTS

Definition of seropositivity

Overall, 71 (4.9 per cent) of 1,451 sera were confirmed as HTLV-I antibody positive. The proportion of screen-positive sera confirmed depended on the initial binding ratio. Thus, 26 (8 per cent) of 313 sera with initial binding ratios 2-2.9 were confirmed as positive, as were 26 (28 per cent) of 92 sera with ratios 3-3.9, 44 per cent of sera with ratios 4-7.9, 69 per cent of sera with ratios 7-10.9, and all sera with ratios in excess of 11. The proportion of screen-

positive sera confirmed as positive (within a specific binding ratio) was the same in each of the studies and did not vary with race, age, socioeconomic status, or other variables.

Seroepidemiology in Panamá City and Colón

A total of 24 (5.7 per cent) of 420 sera collected in Panamá City and 16 (4.9 per cent) of 325 sera collected in Colón were confirmed positive for HTLV-I antibody. Antibody rates did not differ between the two cities in any of the possible risk categories. Therefore, subsequent analyses have combined the two populations. Finally, antibody prevalence rates were the same among aseptic meningitis or conjunctivitis cases and non-cases as well as between case and control families.

Male and female age-specific HTLV-I antibody prevalence rates were highest in adults, but, due to sample selection, few participants in the meningitis survey were older than age 40 years, and statistical comparisons involved small numbers. Male rates peaked in men aged 20-39 years, and female rates were highest in women aged 30 years and older (table 1). However, overall seropositivity rates did not differ statistically between the sexes (Mantel-Haenszel χ^2 test).

We determined race, using standardized criteria, as mestizo, black, white, Oriental,

and Amerind. With the exception of blacks, male rates were greater than female rates (table 2), and rates in men aged 20-39 years were twice as high as those in women aged 20-39 years; however, sample sizes were small and observed differences were not statistically significant.

Socioeconomic indicators and measures of crowding were ascertained during the studies and none were associated with HTLV-I infection (table 3). The association between these variables and HTLV-I was also analyzed controlling for race and age and no differences were apparent.

The Panamá City study gathered information concerning household pets. HTLV-I antibody was more than twice as common in the members of families with household pets (15 out of 183 (8 per cent)) than in families that did not have such pets (nine out of 232 (4 per cent)) (Fisher's exact test $p = 0.05$), but type of pet was not related to HTLV-I infection (nine out of 115 dog owners, three out of 25 cat owners, and three out of 43 owners of other pets); pri-

TABLE 2
Prevalence of HTLV-I antibody by sex, age, and race in Panamá City and Colón, Panamá

Race* and age (years)	Male		Female	
	No.	%	No.	%
Mestizo				
1-19	6/112	5.4	5/144	3.5
20-39	6/57	10.5	7/120	5.8
40+	1/16	6.3	4/27	14.8
Total	13/185	7.0	16/291	5.5
Black				
1-19	0/35	0.0	3/45	6.7
20-39	2/23	8.7	2/44	4.5
40+	0/12	0.0	1/20	5.0
Total	2/70	2.9	6/109	5.5
White				
1-19	0/15	0.0	0/12	0.0
20-39	2/10	20.0	0/23	0.0
40+	0/8	0.0	0/6	0.0
Total	2/33	6.1	0/41	0.0

* Race was unknown for four males and two females. Two males and eight females were Amerind.

TABLE 1

Prevalence of anti-HTLV-I by sex and age in Panamá City and Colón, Panamá

Age (years)	Males		Females	
	No.	%	No.	%
1-9	3/91	3.3	4/109	3.7
10-19	4/76	5.3	4/95	4.2
20-29	6/50	12.0	2/115	1.7
30-39	4/41	9.8	7/78	9.0
40+	1/36	2.8*	5/54	9.3*
Total	18/294	6.1	22/451	4.9

* Only one male older than age 39 years was sampled in Panamá City.

† No females from Panamá City were older than 39 years.

TABLE 3
Prevalence of anti-HTLV-I by socioeconomic variables in Panamá City and Colón, Panamá

Variable	Socioeconomic level			No. of unknown socioeconomic level
	Poor	Low middle	Middle and upper	
Monthly household income	<\$75 (4/71, 5.6%*)	\$75-400 (21/429, 4.9%)	\$500+ (15/234, 6.4%)	11
Household crowding	6+ per room (9/199, 4.5%)	3-5 per room (23/380, 6.1%)	1-2 per room (8/166, 4.8%)	0
Type of house	Shanty (2/64, 3.1%)	Multifamily (16/352, 4.5%)	Single family (18/264, 6.8%)	65

* No. positive/no. tested and % positive.

mates were not kept as pets in any study household.

There was no evidence for household or neighborhood clustering of HTLV-I infection. Only three families had more than one seropositive individual detected. In one such family, both male and female heads-of-household were seropositive, but their three children, ages two, nine, and 11 years, did not have antibody. In the other two families, the female head-of-household had antibody, as did one child in each, age six years in one family and 11 years in the other family, but three other children in one family (12, 13, and 15 years) and two children in the other family (four and nine years) were seronegative. Thirty of the remaining seropositive persons resided in homes with at least one seronegative family member. Five of the seropositive persons were children younger than age 15 years with at least two seronegative siblings also younger than age 15 (we did not obtain sera from their parents). Seven other seropositive children younger than age 15 years had at least two siblings and one parent who tested as negative. Finally, 18 seropositive subjects were adult heads-of-household (11 women and seven men) with at least two seronegative children younger than age 15 years, and eight also had a seronegative spouse.

Female sexual risk factors for HTLV-I infection

We also analyzed seroepidemiologic data from two cervical cancer studies. Ten (3.8 per cent) of 262 women employed at the National Lottery in Panamá City and 21 (4.7 per cent) of 444 women from Herrera Province had HTLV-I antibody. In Herrera Province, HTLV-I prevalence was the same in cervical cancer cases and controls. Race-, age-, and income-specific antibody rates were similar to those observed in the Panamá City or Colón populations. In both cervical cancer studies, HTLV-I antibody was associated with the number of sexual partners (table 4) but was not associated with age at first intercourse, age at first marriage, age at first pregnancy, or number of pregnancies.

These two studies elicited information concerning a variety of other variables, none of which were associated with HTLV-I infection. Variables included: history of hospitalization during childhood, adolescence, and adulthood; family history of major illness, cancer or early death (with family defined as mother, father, siblings, spouse, children); habitual use of pharmaceuticals; and smoking and drinking histories.

In both studies, women with a history of

TABLE 4

Relation of HTLV-I antibody and sexual experience among women in two cervical cancer studies, Herrera Province and National Lottery employees in Panamá City, Panamá

No. of lifetime sexual partners*						No. of marriages†					
1		2		3+		1		2		3+	
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
16/409‡	3.9§	7/142	4.9	8/137	5.8	19/460	4.1	6/136	4.4	6/81	7.4

* For 18 subjects, number of sexual partners was unknown.

† For 29 subjects, number of marriages was unknown.

‡ No. positive/no. tested.

§ % positive.

herpes zoster (positive response to the question, "Have you ever had shingles?") were significantly more likely to have HTLV-I antibody (5/28 (18 per cent)) than women who said they hadn't had herpes zoster (26/654 (4 per cent)) ($\chi^2 = 8.9$, $p = 0.003$), or women with a history of recurrent oral herpes (3/165 (2 per cent)). No woman gave a history of genital herpes disease, and there was no relation between herpes type 2 seropositivity (measured by microneutralization) and HTLV-I infection.

DISCUSSION

Our studies revealed that 5 per cent of Panamá City and Colón residents had HTLV-I antibody. This is similar to rates observed elsewhere, i.e., Kingston, Jamaica, where 4–10 per cent of normal individuals are seropositive (15), Venezuela, with 7 per cent seropositivity (16), and parts of equatorial Africa with rates of 4–31 per cent (14, 17–18). We believe that our study is the first to analyze HTLV-I infection in three major racial groups (defined by standard criteria) which reside in the same geographic area. We did not detect racial differences, and this implies that the high HTLV-I infection rates in Jamaica and Africa are not primarily attributable to racial factors. In addition, the high infection rates in Panamá support the hypothesis that HTLV-I is endemic throughout the Caribbean Basin. More extensive studies are in progress to define race- and ethnic

group-specific HTLV-I infection rates throughout Panamá.

Unfortunately, we do not have complete data concerning adult T-cell lymphoma occurrence in Panamá with which to round out this seroepidemiologic study. HTLV-I-associated adult T-cell lymphoma is a major hematologic malignancy in both Japan and Jamaica (6, 19), and we would expect the disease to be common in metropolitan Panamá. However, an ongoing clinical study in Panamá City has not yet documented adult T-cell lymphoma (W. C. Reeves, unpublished data).

Male and female age-specific HTLV-I infection rates in Panamá were similar to those in other endemic areas (6, 15, 17). Three per cent of Panamá City and Colón children younger than age 10 years had been infected. This rate is similar to the rate in Jamaica, where nine (2.1 per cent) of 432 subjects younger than age 19 years had antibody (15) and is comparable with rates in Ghana, where 3–8 per cent of children aged 1–10 years were seropositive (14, 17). Sera from the Panamá, Jamaica, and Ghana studies were screened and confirmed in the same laboratory by the same assay (ELISA), so that results are comparable. This pattern of seropositivity implies stable endemic HTLV-I transmission in the three populations.

Studies from several geographic areas have yielded conflicting data concerning the relation between sexual risk factors and HTLV-I infection. In our study, infection

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differ between HTLV-I antibody positive or negative subjects. Cervical cancer, which may be a virally induced chronic disease, was not associated with HTLV-I infection. However, herpes zoster, a disease caused by reactivation of a latent deoxyribonucleic acid (DNA) virus, was significantly more common in women with HTLV-I antibody.

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