Seroprevalence and risk factors for human T-cell lymphotropic virus (HTLV-I) infection among ethnically and geographically diverse Peruvian women

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Objective: To assess the seroprevalence and risk factors for HTLV-I infection in Peruvian women.

Methods: Five hundred and sixty-eight healthy women > 20 years of age from three Peruvian regions were randomly selected and screened for HTLV-I. ELISA-reactive sera were confirmed via immunofluorescence assay, recombinant immunoblot assay, Western blot, and PCR. Women from Huanta (n=303), an Andean city inhabited by indigenous Quechuans; El Carmen (n=132), a primarily African-American coastal town; and Lima (n=133), with its Mestizo population, were selected.

Results: HTLV-I antibodies were present in 2.5% (14/568) of women (1.3% in Huanta, 3.8% in El Carmen, and 3.8% in Lima); 2.5%, 2.7% and 2.6% of Quechuans, Mestizas and African-Americans, respectively, were infected. History of a blood transfusion (P < 0.00002), chronic scabies (P < 0.02), having a relative with leukemia (P < 0.04), age ≥ 38 years (P < 0.03), young age at first intercourse (P < 0.04), lifetime partners > 4 (P < 0.04), educational status (P < 0.02) and > 4 pregnancies (P < 0.03) were significantly associated with infection.

Conclusions: HTLV-I is endemic among asymptomatic Peruvian women. Parenteral, vertical and heterosexual transmission are associated with infection.


INTRODUCTION

The human T-cell lymphotrophic viruses (HTLV) are associated with two main clinical entities: adult T-cell leukemia/lymphoma (ATLL), and HTLV-I-associated myelopathy (HAM) or tropical spastic paraparesis (TSP). HTLV is endemic in Japan, the Caribbean, equatorial Africa, Latin America, north-eastern Iran, Melanesia, and the Solomon Islands, and among Australian Aborigines. The highest prevalence rates for HTLV-I have been documented in south-western Japan (17%) and in the Caribbean basin (4-9%); in the USA, the rate is 0.016-0.1%. HTLV-I has infected an estimated 10-20 million individuals worldwide, but precise figures are not available. HTLV-I is highly cell-associated, and requires the passage of infected lymphocytes to noninfected individuals, whereas HIV can be transmitted extracellularly. HTLV-I is transmitted through sexual intercourse, whole blood, or cellular blood products, and vertically from mother to child, postnatally via breastfeeding. Currently, there is a lack of evidence for intrauterine or perinatal infection with HTLV-I.

People of African origin have a higher prevalence of HTLV-I than other populations in the same hyperendemic regions of comparable socioeconomic status. A preferential geographic focus in the Andes for HTLV-I infection has been suggested by various studies. The transmission mechanisms in HTLV-I infection are incompletely understood, since: (1) HTLV-I is found almost exclusively in tropical areas of the world; (2) there is evidence for both familial and neighborhood clustering among cases; and (3) in people migrating from endemic to non-endemic areas, HTLV-I seropositivity declines in subsequent generations. Japanese people infected by HTLV-I have a higher rate of ATLL (4% cumulative lifetime risk) and a lower rate of TSP (0.25%) than individuals infected by HTLV-I have a higher rate of ATLL (4% cumulative lifetime risk) and a lower rate of TSP (0.25%) than people infected by HTLV-I have a higher rate of ATLL (4% cumulative lifetime risk) and a lower rate of TSP (0.25%).

Based on a cohort study conducted in Miyasaki, Japan, the seroprevalence curve for HTLV-I demonstrates a parallel increase in seropositivity for men and women until age 55 (at 25%), followed by a plateauing effect among men and a continued increase among women (to 52%). Similar results have been reported...
in other studies. HTLV-I infection was also associated with low socioeconomic status, lack of education, and the practice of prostitution, among other factors.

The objective of this study was to investigate HTLV-I infection in Peru among healthy, asymptomatic women more than 20 years of age who did not practice high-risk behaviors for acquiring HTLV-I infection. Second, we assessed whether HTLV-I infection rate varied with geographic and/or ethnic diversity. Third, we assessed risk factors that predispose to HTLV-I infection.

MATERIALS AND METHODS

This study was conducted in three regions of Peru: Huanta, El Carmen, and Lima. The Andean city of Huanta is located at an altitude of 2400 m, and is inhabited by an indigenous Quechuan population (26,741 inhabitants). El Carmen is a Pacific coastal town located 200 km south of the capital city of Lima, and is inhabited predominantly by an African-American population (total population 10,980). Lima is the capital of Peru; it is located on the Pacific coast, and is inhabited by 7 million people. The majority of the population is considered to be 'Mestizo,' a mix of Spanish and indigenous Indian blood. The 'North Cone', the neighborhood where this study was conducted, is inhabited by a Mestizo population of low socioeconomic status.

Based on our sample sizes and village population sizes, we were able to detect with 99% accuracy a true population prevalence of at least 2–5%. Based on census data calculations, 4.3% (n = 303) of women >20 years of age were sampled in Huanta, and 5.6% (n = 132) of women >20 years of age were sampled in El Carmen. Since Huanta and El Carmen are divided into census squares, each census square was selected in a blinded fashion, and women were enrolled into the study via a household visit. Random sampling was ensured by indiscriminately selecting women from different census tracts. In Lima, healthy women from the ‘North Cone’ >20 years of age who brought their children for routine immunizations to the Cayetano Heredia Hospital were enrolled.

Human subjects approval was obtained from Stanford University and Cayetano Heredia University. The purposes of our study were explained, and those women who provided written or oral (for the illiterate) informed consent were enrolled. A detailed questionnaire was orally administered in Spanish or Quechua, indigenous Indian blood. The East Cone, the neighborhood where this study was conducted, is inhabited by a Mestizo population of low socioeconomic status.

RESULTS

In total, 568 women were enrolled in this study. Table 1 shows the demographic characteristics of the subjects studied: 23.2% (n = 132) were from El Carmen (African-American), 53.3% (n = 303) from Huanta (indigenous), and 23.4% (n = 133) from Lima (Mestizo). The ages ranged between 20 and 82 years. The racial distribution of the volunteers included 34.8% (n = 198) Quechuans, 46.5% (n = 264) Mestizas, 13.4% (n = 76) African-American, and 5.3% (n = 30) Mestizo-African-American. Of the total enrolled, 38.9% (n = 220) were born on the coast, 59.4% (n = 337) in the Andes, and only 1.8% (n = 10) in the jungle area.

HTLV-I antibodies were demonstrated in 2.5% (14 of 568) of asymptomatic women from El Carmen, Huanta, and Lima. No cases with HTLV-II infection were detected in this study.

Assessment of HTLV-I seropositivity per geographic location yielded the following results: 3.8% (5 of 132) for El Carmen, 1.3% (4 of 303) for Huanta, and 3.8% (5 of 133) for Lima. These differences were non-significant. Seropositivity for HTLV-I increased with age, but this increase was found to be non-significant. According to birthplace (Table 1), 2.1% of those born in the Andes were HTLV-I-infected compared to 3.2% of those born in the coastal region and 0% of those born in the jungle. The rates of HTLV-I infection according to ethnicity were 2.5% (5 of 198) in the Quechuans, 2.7% (7 of 264) in Mestizos, 2.6% (2/76) in African-Americans, and 0% (0 of 30) in the Mestizo-African-American population; these differences were found to be non-significant.

Among the subjects from El Carmen who had at least one Andean parent, 25% (3 of 12) were infected compared to 0.4% of those who did not have an Andean parent (OR 19.7, P < 0.005). In Lima, this factor was found to be non-significant.

Factors that were significantly associated with HTLV-I infection in our study were the following (Table 2); history of a blood transfusion (P < 0.00002, OR 13.1), having had an episode of chronic scabies (P < 0.02, OR 13.0), having had a relative with leukemia or lymphoma (P < 0.04, OR 4.8), age at first intercourse less than or
No significant association was demonstrated between HTLV-I infection and frequent use of intramuscular injections, having undergone a surgical procedure or Caesarean section, having had a history of hepatitis or jaundice, a parasitic infection, or a sexually transmitted disease (STD), or having been breastfed for longer than 6 months or 1 year. Although the presence of these risk factors was associated with a higher rate of infection, these differences were found to be non-significant. Only 3.7% of women studied reported an STD history. A history of genital ulcer was reported by 5.5%, having had a partner with an STD by 1.5%, and having had a partner with a genital ulcer by 2.2%; however, none of these women was HTLV-I-infected.

**DISCUSSION**

There have been reports of high HTLV-I infection rates in South America; however, this is the largest study conducted in Peru among asymptomatic women from three different ethnic groups and geographic regions. Our study complements a recent study in Ouillahamba, Peru, an Andean region, which found HTLV-I infection rates of 2.3% in healthy pregnant women (n=211), 13.7% in FSWs, and 8.5% in STD patients. In our study, a seropositivity rate of 2.5% (14 of 568) was found among women studied. Specifically, infection rates were 3.8% for El Carmen and Lima, and 1.3% for Huanta (Andes). These rates are significant, and confirm that HTLV-I infection is an important public health problem in Peru. HTLV-I infection occurs not only among high-risk groups (i.e. FSWs, STD carriers), but also in healthy, asymptomatic women. HTLV-I infection rates in Peru are similar to those found in other endemic areas of the world, but not as high as in Okinawa (15%).

Sonoda et al have described two mutually exclusive HLA haplotypes associated with HTLV infection, suggesting that distinct haplotypes could determine susceptibility patterns to infection by HTLV-I or HTLV-II. The first haplotype was found among South American Andes natives and Japanese with exclusive infection by HTLV-I, while the second was found among Orinoco River natives in Peru. In this study, the infection rate was 2.5% (14 of 568), which is similar to the rates found in other studies conducted in Peru. The factors associated with HTLV-I infection in this study are listed in Table 2.

**Table 2. Factors associated with human T-cell lymphotropic virus type-I (HTLV-I) infection among healthy, asymptomatic women in Peru (n=568)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>HTLV-I positive/Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>8/59 (13.6)</td>
</tr>
<tr>
<td>Severe resistant scabies</td>
<td>2/9 (22.2)</td>
</tr>
<tr>
<td>Relative with leukemia/lymphoma</td>
<td>0/3 (0.0)</td>
</tr>
<tr>
<td>Age at first intercourse ≤20 years</td>
<td>13/385 (3.4)</td>
</tr>
<tr>
<td>Number of sexual partners in life &gt;4</td>
<td>2/13 (15.4)</td>
</tr>
<tr>
<td>Age &gt;38 years</td>
<td>10/229 (4.4)</td>
</tr>
<tr>
<td>Years of education ≤7</td>
<td>12/302 (4.0)</td>
</tr>
<tr>
<td>Pregnant &gt;4 times</td>
<td>9/211 (4.3)</td>
</tr>
</tbody>
</table>

In conclusion, HTLV-I infection is a common disease in Peru, affecting 2.5% of the population. The factors associated with HTLV-I infection are listed in Table 2, and include blood transfusion, severe resistant scabies, relative with leukemia/lymphoma, age at first intercourse ≤20 years, number of sexual partners in life >4, age >38 years, years of education ≤7, and pregnant >4 times. These factors are significant and should be considered when planning interventions to control HTLV-I infection in Peru.

**Table 1. Demographic characteristics and HTLV-I seropositivity according to geographic location, ethnicity, age, and birthplace (n=568)**

<table>
<thead>
<tr>
<th>Geographic location</th>
<th>Number/Total (%)</th>
<th>HTLV-I positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>El Carmen</td>
<td>132/568 (23.2)</td>
<td>5/132 (3.8)</td>
</tr>
<tr>
<td>Huanta</td>
<td>303/568 (53.3)</td>
<td>4/303 (1.3)</td>
</tr>
<tr>
<td>Lima</td>
<td>133/568 (23.4)</td>
<td>5/133 (3.8)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quechua</td>
<td>198/568 (34.8)</td>
<td>5/198 (2.5)</td>
</tr>
<tr>
<td>Mestizo</td>
<td>264/568 (46.5)</td>
<td>7/264 (2.6)</td>
</tr>
<tr>
<td>African-American</td>
<td>r/b566 (13.4)</td>
<td>2/16 (12.6)</td>
</tr>
<tr>
<td>Mestizo/African</td>
<td>30/568 (5.3)</td>
<td>0/30 (0.0)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-30 years</td>
<td>131/564 (23.2)</td>
<td>2/131 (1.5)</td>
</tr>
<tr>
<td>31-40 years</td>
<td>266/564 (47.2)</td>
<td>6/266 (2.3)</td>
</tr>
<tr>
<td>41-50 years</td>
<td>94/564 (16.7)</td>
<td>3/94 (3.2)</td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>73/564 (12.9)</td>
<td>7/73 (9.6)</td>
</tr>
<tr>
<td>Place of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coast</td>
<td>220/567 (38.9)</td>
<td>7/220 (3.2)</td>
</tr>
<tr>
<td>Andes</td>
<td>337/567 (59.4)</td>
<td>7/337 (2.1)</td>
</tr>
<tr>
<td>Jungle</td>
<td>10/567 (1.8)</td>
<td>0/10 (0.0)</td>
</tr>
</tbody>
</table>
natives in the lowlands of South America and North American Indians with exclusive infection by HTLV-II. In a second phylogenetic study of South American natives, HLA haplotypes among HTLV-I and HTLV-II carriers were found to be mutually segregated, representing genetic backgrounds that could account for differing susceptibilities to HTLV. This could explain the presence of segregated foci of HTLV-I infection in the Andes highlands among Quechuan natives and HTLV-II infection in the Orinoco lowlands of Colombia among the Guahibo Indians. Our study with the Quechuan population confirmed the exclusive presence of HTLV-I.

Our study found a 2.6% infection rate among the African-American women surveyed. Gessain et al found virtually identical sequences between isolates from West Africa, the Ivory Coast and the Central African Republic and those from the French West Indies, Haiti, French Guyana and Peru. One theory included an ancient introduction from mongoloid migrations. The second hypothesis argues for a post-Columbian introduction of HTLV-I from Africa into the western hemisphere as a result of the slave trade about 350 years ago, and a more recent migration of HTLV I infected Japanese to America.

Of the HTLV-I-infected subjects, 50% (7/14) had been born in the Andean region (35.7% in El Carmen and 14.3% in Lima). This correlates well with our initial findings that linked HTLV-I infection with birth in the Andean region. Among TSP patients in Lima, 48% had been born in the Andes, while 68% had lived a significant proportion of their lives in this same region. In HTLV-I-associated Strongyloides stercoralis-infected patients presenting in Lima, almost 50% were born in the Andes region. In the coastal city of El Carmen, having at least a father or mother from the Andes was significantly associated with an increased HTLV-I infection rate (P < 0.005). The infection rate found in Lima (3.8%) in the ill mestizo population represents migration of Quechuans to the capital city, making a new endemic region. This study confirms that the Andean Valley is endemic for HTLV-I.

History of a blood transfusion was significantly associated with HTLV-I infection, such that 13.6% of people who had received a blood transfusion were HTLV-I infected (P < 0.00002), compared to 1.2% who had not. This is a plausible transmission route, considering that, at the time of this study, blood in Peru was not being screened for anti-HTLV-I antibodies prior to transfusion. Japan, with its high prevalence of HTLV-I, as well as low-prevalence areas such as the USA and Europe, is currently screening for anti-HTLV-I antibodies. Blood transfusion was reported as a risk factor for infection with HTLV-I, as has been described in series of TSP/HAM patients.

Heterosexual transmission appears to be another route of HTLV-I transmission among the Peruvian women studied. This is supported by the fact that early age at first intercourse (≤20 years, P < 0.04), having more than four sexual partners in life (P < 0.04), and multiparity (being pregnant >4 times, P < 0.03), were significantly associated with infection. Early age at first intercourse might imply a greater number of lifetime sexual partners as well as longer duration of relationship with the same seropositive partner, which have been found to be associated with increased risk of HTLV-I transmission. Furthermore, condoms were being used by only 6.5% (n = 37) of the women surveyed. Also, IUD use has been associated with increased HTLV-I infection, and is considered to represent a high risk for retroviral infection, secondary to its association with pelvic infections and the fact that mucosal alterations and a high level of lymphocytic infiltration of the cervix or uterus occur with an IUD in place; however, none of these patients was using an IUD. In addition, anatomic differences may increase the efficiency of male-to-female HTLV-I transmission. Many studies report STDs as being significantly associated with HTLV-I infection. In our study, only 3.7% of women reported having an STD.

Being 38 years or more of age (mean age 38.6) was significantly associated with increased HTLV-I infection (P < 0.01). In other series, the seropositivity increased with age, probably due to more risk and cumulative risk as a result of sexual exposure, or by the cohort effect. In different Peruvian studies, we have demonstrated that age is an important factor.

Having a relative with leukemia or lymphoma was a significant risk factor for HTLV-I infection (OR 4.8, P < 0.04). In our study, 9.4% of patients having a relative with leukemia or lymphoma were infected, compared to 2.1% of women without relatives with leukemia (P < 0.04). HTLV-I is associated with ATLL in Japan and Latin America. HTLV-I has been associated with an immunosuppressive state. Crusted (Norwegian) scabies is a rare form of scabies that affects the immunosuppressed host. Some reports have associated crusted scabies and HTLV-I seropositivity. One study found all patients with crusted scabies to be HTLV-I positive. In our study, a significant correlation between HTLV-I infection and severe resistant scabies was found (P < 0.02).

Besides the known endemicity of HTLV-I in Japan, Africa, and the Caribbean, this study confirms that HTLV-I infection is endemic in Peru and is an important public health problem, currently under-recognized.

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REFERENCES


