Frequent HTLV-1 infection in the offspring of Peruvian women with HTLV-1–associated myelopathy/tropical spastic paraparesis or strongyloidiasis

Eduardo Gotuzzo,[1] *Joel Moody,*[2] *Kristien Verdonck,*[1,3] *Miguel M. Cabada,*[1] *Elsa González,*[1] *Sonia Van Dooren,*[4] *Anne-Mieke Vandamme,*[4] *Angélica Terashima,*[1] *and Sten H. Vermund*[5]

Suggested citation Gotuzzo E, Moody J, Verdonck K, Cabada MM, González E, Van Dooren S, et al. Frequent HTLV-1 infection in the offspring of Peruvian women with HTLV-1–associated myelopathy/tropical spastic paraparesis or strongyloidiasis. Rev Panam Salud Publica. 2007;22(4):223–30.

ABSTRACT

Objectives. *To describe the frequency of HTLV-1 infection among offspring of mothers who had presented with HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP), strongyloidiasis, or asymptomatic HTLV-1 infection, and to identify factors associated with HTLV-1 infection.*

Methods. *In a descriptive study, records were reviewed of HTLV-1–positive women and their offspring who had been tested for HTLV infection at a public hospital in Lima, Peru, from 1989 to 2003. Sons and daughters of women who had presented with strongyloidiasis, HAM/TSP, or asymptomatic infection were eligible for this study.*

Results. *Three hundred seventy subjects were included: 279 were the offspring of 104 mothers presenting with HAM/TSP, 58 were the offspring of 22 mothers with strongyloidiasis, and 33 were the offspring of 26 asymptomatic mothers. Mean age of the offspring at the time of testing was 26 years (standard deviation 12). Nineteen percent of the offspring tested positive for HTLV-1: 6% (2/33) of those with asymptomatic mothers, 19% (52/279) among the offspring of mothers with HAM/TSP, and 31% (18/58) among the offspring of mothers presenting with strongyloidiasis On multiple logistic regression analysis, three factors were significantly associated with HTLV-1: (a) duration of breast-feeding (odds ratio [OR] = 15.1; [4.2–54.1] for 12 to 24 months versus less than 6 months breast-feeding); (b) clinical condition of the mother (OR = 8.3 [1.0–65.3] for HAM/TSP and OR = 11.5 [1.4–98.4] for strongyloidiasis in comparison with offspring of asymptomatic mothers); and (c) transfusion history (OR = 5.5 [2.0–15.2]).*

Conclusions. *In addition to known risk factors for HTLV-1 transmission (duration of breast-feeding and history of blood transfusion), maternal HAM/TSP and strongyloidiasis were associated with seropositivity among offspring of HTLV-1–infected mothers.*

[1] Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru. Send correspondence to: Eduardo Gotuzzo, Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Av. Honorio Delgado 430, Lima 31, Peru; telephone: 005114823910; fax: 004114823404; e-mail: egh@upch.edu.pe

[2] Division of Geographic Medicine, University of Alabama at Birmingham, Birmingham, Alabama, U.S.A.

[3] Virology Unit, Department of Microbiology, Institute of Tropical Medicine, Antwerp, Belgium.

[4] REGA Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium.

[5] Institute for Global Health, Vanderbilt University School of Medicine, Nashville, Tennessee, U.S.A.

Key words Breast feeding; disease transmission, vertical; human T-lymphotropic virus 1; HTLV-1–associated myelopathy; HTLV-1 infections/transmission; offspring; paraparesis, tropical spastic; strongyloidiasis; Peru.

Since the first description of human T-lymphotropic virus 1 (HTLV-1) in 1980 (1), multiple studies have demonstrated that the major routes of transmission are from mother to child (2, 3), through sexual intercourse (4), transfusion of cellular blood components (5), and sharing of needles and syringes among injecting drug users (6). In HTLV-1–endemic areas, mother-to-child transmission is considered to be the most important factor sustaining endemicity, as suggested in reports from Japan, Africa, the Caribbean, and South America (7).

Mother-to-child transmission of HTLV-1 occurs most often through breast-feeding; both transplacental and intrapartum infection have been reported only rarely (3, 8). The rate of mother-to-child transmission ranges from 6% to 38% (3, 9). The risk of transmission increases with longer duration of breast-feeding (9), higher provirus load in peripheral blood mononuclear cells and in breast milk (10, 11), and the concordance of human leukocyte antigens (HLA) class I between mother and child (12). It is not known whether there is also an association between maternal HTLV-1–associated diseases and mother-to-child transmission.

In Peru, an estimated 1% to 3% of healthy adult women are carriers of HTLV-1 (13, 14). Since 1989, the Hospital Nacional Cayetano Heredia and the Institute of Tropical Medicine Alexander von Humboldt of the Universidad Peruana Cayetano Heredia have served as a reference center for diagnosis and follow-up of people infected with HTLV-1.

HTLV screening of blood donors has been obligatory in Peru since 1998 (15, 16). Several blood banks refer seropositive candidate blood donors to the Institute of Tropical Medicine Alexander von Humboldt for counseling and follow-up. In addition, patients with a presumptive diagnosis of HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) have been regularly referred from three major public hospitals (17). While HTLV-2 can also cause neurological disease, it appears to be less common than HTLV-1 infection in Lima (18, 19). In several prevalence studies, no cases of HTLV-2 were found (13, 14).

Infection with *Strongyloides stercoralis* is a frequent motive for HTLV-1 testing in this setting. Previously, we have linked HTLV-1 to *Strongyloides stercoralis* hyperinfection and relapse after ivermectin or thiabendazole treatment (20, 21). There is now epidemiological evidence that HTLV-1 is also associated with strongyloidiasis in general. Based on a Japanese cohort study, it is estimated that the risk of developing strongyloidiasis is twice as high for HTLV-1–infected people than for seronegative controls (22).

The objectives of this descriptive and retrospective study are (a) to evaluate the frequency of HTLV-1 infection among the offspring of mothers who had presented with HAM/TSP, strongyloidiasis, or asymptomatic HTLV-1 infection, and (b) to identify factors associated with HTLV-1 infection among the offspring.

MATERIALS AND METHODS

Setting

The study was conducted at the Institute of Tropical Medicine Alexander von Humboldt and the Hospital Nacional Cayetano Heredia in Lima, Peru. Beginning in 1989, routine evaluation of people suspected to be infected with HTLV-1 has included a standardized questionnaire administered by trained health workers, a thorough medical evaluation, and HTLV-1 testing. The same procedures are offered to close relatives (parents, spouses, children, and siblings) of those who are seropositive for HTLV-1.

Study population and procedures

For this study, we first reviewed the files of all HTLV-1–positive women who had presented at our institute with HAM/TSP, strongyloidiasis, or asymptomatic HTLV-1 infection between 1989 and 2003. We then checked the files of their offspring and included all subjects with known HTLV-1 status who were at least three years old when they were tested, because before that age, serology is not entirely reliable for the diagnosis of HTLV-1. We did not include offspring of women with other HTLV-1–associated conditions such as adult T-cell leukemia/lymphoma and uveitis because few women with these diseases had been referred to our center before 2003.

The information obtained from the files of the offspring included sex, age at the time of HTLV-1 testing, type of delivery, history of breast-feeding, and HTLV status. Because many of them were adults when they were tested, we also recorded information on other risk factors for HTLV-1 infection, such as blood transfusion, drug use, and history of sexually transmitted infections. Among men, a history of contact with commercial sex workers and same sex contact was also registered. From the files of the mothers, we obtained the motive for HTLV-1 testing, ethnic background, and age at the time of delivery.

In the case of HAM/TSP, clinical diagnosis followed criteria proposed by the World Health Organization (23). The diagnosis of strongyloidiasis was based on direct examination, concentration methods (including Baermann procedure) and/or agar plate culture of stool samples. All patients with strongyloidiasis received standard

treatment with ivermectin or thiabendazole. For HTLV screening, an enzyme immunoassay was used (Sanofi Diagnostics Pasteur, France; Bio-Rad Laboratories, U.S.A.; or Cambridge Biotech, U.S.A.). To confirm the diagnosis and to distinguish between HTLV-1 and HTLV-2, we used western blot (Genelabs Diagnostics, Singapore) or line immunoassay (Innogenetics, Belgium).

Statistical analysis

We first describe the frequency of HTLV-1 infection and of several known risk factors for HTLV-1 infection (history of breast-feeding, blood transfusion, and sexually transmitted diseases, among others) among the offspring of women with asymptomatic HTLV-1 infection, HAM/TSP, or strongyloidiasis. Second, we describe the frequency of HTLV-1 in a subgroup of children who had not received a blood transfusion and who were less than 13 years old when they were tested for HTLV-1. We considered that mother-to-child transmission was the only possible mode of infection in these children.

Finally, analyzing all offspring in the study, we compared the frequency of several factors possibly associated with HTLV-1 transmission in seropositive subjects with the frequency in seronegative subjects. All factors found to occur more frequently among HTLV-1–positive subjects in bivariate calculations ($P < 0.2$) were included in a multiple logistic regression analysis. We decided *a priori* to also include in this model the age of the offspring at the time of HTLV-1 testing. Odds ratios and adjusted odds ratios with 95% confidence interval, indicating strength of association of the included factors with seropositivity among offspring, were calculated using SPSS 13.0 for Windows (SPSS Inc., Chicago, Illinois, U.S.A.).

Ethical considerations

The study protocol was approved by the Institutional Ethics Committee of the Universidad Peruana Cayetano Heredia and the study was conducted following the guidelines of this university with respect to protection of human participants.

RESULTS

One hundred fifty-two HTLV-1–positive mothers were identified during the study period: 104 (68%) had a diagnosis of HAM/TSP, 22 (14%) had *Strongyloides stercoralis* infection, and 26 (17%) were asymptomatic carriers of the virus. Their mean age at the time of delivery was 27 years (standard deviation [SD] 7) and at the time of HTLV-1 testing was 51 years (standard deviation 13). These mothers had 641 children. Of these offspring, 468 (73%) had mothers with HAM/TSP, 98 (15%) had mothers with strongyloidiasis, and 75 (12%) had asymptomatic mothers. Of these offspring, 383 (60%) attended the study center and were tested for HTLV-1. Seven children were less than three years old when they were tested and six persons had indeterminate HTLV-1 results, so these 13 subjects (2%) were excluded from the study. Of the remaining 370 subjects included in the analysis, 279 (75%) were sons or daughters of mothers with HAM/TSP, 58 (16%) of mothers with strongyloidiasis, and 33 (9%) of asymptomatic mothers. None of the mothers or the offspring tested positive for HTLV-2.

The characteristics of the offspring are shown in Table 1. There were 156 (42%) male and 214 (58%) female subjects. Their mean age at the time of HTLV-1 testing was 26 years (SD 12). Offspring of mothers with HAM/TSP were significantly older than those of

TABLE 1. Characteristics of offspring of HTLV-1–positive mothers, according to mothers' clinical condition, Peru

Characteristic	Offspring of asymptomatic carriers (n = 33)	Offspring of women with HAM/TSP (n = 279)	Offspring of women with strongyloidiasis (n = 58)
Mean age at time of HTLV-1 testing: years (95% CI)	18.9 (14.6–23.3)	27.0 (25.7–28.3)[a]	23.3 (19.6–26.9)
Mean maternal age at delivery: years (95% CI)	25.3 (23.3–27.4)	27.2 (26.4–28.1)	25.5 (23.9–27.2)
	Percentage with the characteristic (95% CI)		
HTLV-1 seropositive	6% (0%–14%)	19% (14%–23%)	31% (19%–43%)[b]
Male sex	39% (23%–56%)	42% (36%–48%)	43% (30%–56%)
Breast-feeding:[c]			
< 6 months	23% (8%–38%)	24% (19%–29%)	22% (11%–33%)
6 to < 12 months	17% (3%–30%)	26% (21%–31%)	16% (6%–26%)
12 to < 24 months	43% (26%–61%)	42% (36%–48%)	48% (34%–62%)
≥ 24 months	17% (3%–30%)	8% (5%–11%)	14% (4%–24%)
Vaginal delivery	97% (90%–100%)	94% (91%–96%)	96% (91%–100%)
History of blood transfusion	3% (0%–9%)	8% (5%–11%)	5% (0%–11%)
Males ≥ 18 years:	n = 6	n = 89	n = 16
With history of STD	17% (0%–64%)	21% (13%–30%)	38% (14%–61%)
With history of sexual contact with man	20% (1%–72%)	8% (2%–13%)	6% (0%–30%)
With history of sexual contact with female worker	40% (5%–85%)	52% (41%–63%)	44% (19%–68%)
Females ≥ 18 years:	n = 9	n = 131	n = 17
With history of STD	11% (0%–48%)	3% (1%–8%)	0% (0%–20%)

Note: HAM/TSP: HTLV-1–associated myelopathy/tropical spastic paraparesis; CI: confidence interval; STD: sexually transmitted disease.

[a] $P < 0.01$ in comparison with offspring of asymptomatic mothers; two-sample t test.

[b] $P < 0.05$ in comparison with offspring of asymptomatic mothers; chi-square test (continuity correction).

[c] Data on breast-feeding duration were available for 343 of 370 subjects.

asymptomatic mothers (27 versus 19 years; $P < 0.01$). Data on the duration of breast-feeding could be obtained in 343 of 370 subjects (93%). Of these, 12 (3%) were never breast-fed, 69 (20%) were breast-fed for less than 6 months, and 262 (76%) for 6 months or more.

Twenty-six subjects (7%) had received a blood transfusion before they were tested for HTLV-1. There were no commercial sex workers or injecting drug users among the participants. One hundred eleven men were 18 years or older at the time of testing. Fourteen percent had used drugs (marihuana and/or crack), 23% had a history of a sexually transmitted infection, 50% admitted contact with a commercial sex worker, and 8% had had sex with other men. There were 157 women who were 18 years or older at the time of testing; 3% had used drugs and 3% had a history of a sexually transmitted infection (Table 1).

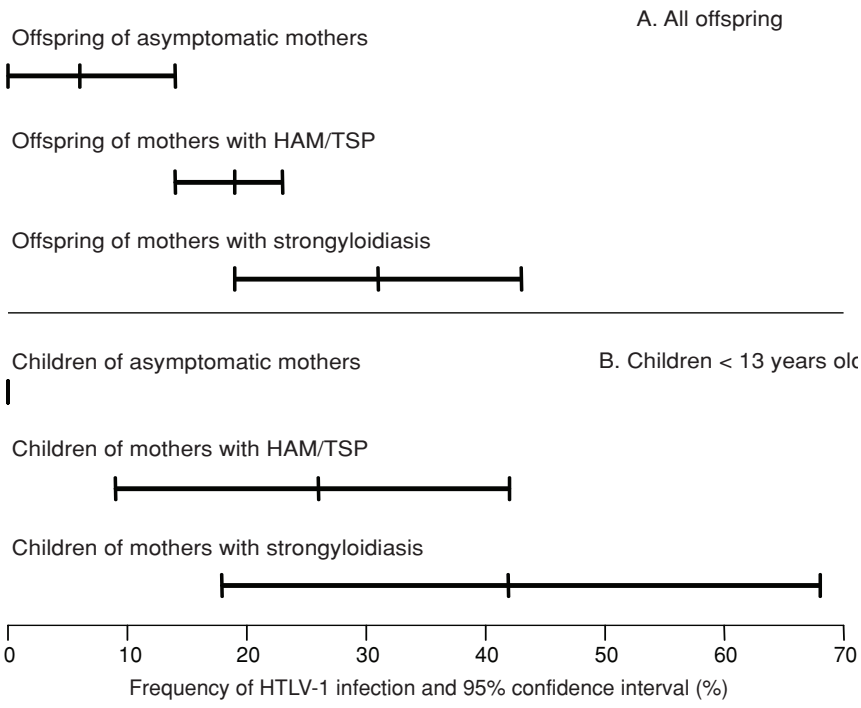
Seventy-two (19%) of the 370 participants were seropositive for HTLV-1: 2 (6%) were among the 33 offspring of asymptomatic mothers; 52 (19%) were among the 279 offspring of mothers with HAM/TSP; and 18 (31%) were among the 58 offspring of mothers with strongyloidiasis (Figure 1). Fifty-eight children had not received a blood transfusion and were younger than 13 years when they were tested. In this subgroup, there were 13 (22%) seropositive children: 0 of 15 children of asymptomatic mothers, 7 (26%) of 27 children of mothers with HAM/TSP, and 6 (38%) of 16 children of mothers with strongyloidiasis (see Figure 1). Among these children, 3 (13%) of 24 boys and 10 (29%) of 34 girls were infected ($P = 0.2$).

In bivariate analysis, there was an association between HTLV-1 infection and duration of breast-feeding (Table 2). The frequency of HTLV-1 infection was 4% (3/81) among subjects who had been breast-fed for less than 6 months, 15% (12/81) for those breast-fed for 6 to 12 months, 28% (42/148) for those breast-fed 12 to 24 months, and 33% (11/33) for subjects who were breast-fed for 24 months or longer (chi-square for trend: $P < 0.01$). In the HTLV-1–positive group, there were more subjects with a history of a blood transfusion (odds ratio [OR], 3.1; 95% confidence interval [CI], 1.4–7.0) and more offspring of mothers of Andean background (OR, 2.1; 95% CI, 1.2–3.9) than in the HTLV-1–negative group. The association between HTLV-1 seropositivity and the clinical condition of the mother was also significant (OR, 7.0; 95% CI, 1.5–32.4) for offspring of mothers with strongyloidiasis compared to offspring of asymptomatic carriers (Table 2). The frequency of HTLV-1 infection according to the clinical condition of the mothers and the duration of breast-feeding is shown in Figure 2.

We found no associations between the HTLV-1 status of the offspring and maternal age at delivery, type of delivery, age at the time of testing, history of drug use, of sexually transmitted infections, contact with a commercial sex worker, or same-sex contact.

In the multiple logistic regression analysis, HTLV-1 infection in offspring of infected mothers was associated with: (a) the duration of breast-feeding, (b) the clinical condition of the mother, and (c) a history of blood transfusion. The adjusted OR was 5.7 (95% CI, 1.5–22.2) for 6 to 12 months of breast-feeding compared with less than 6 months; for 12 to 24 months the adjusted OR was 15.1 (95% CI, 4.2–54.1); and for 24 months or more the adjusted OR was 18.8 (95% CI 4.4–79.8). For the mothers' clinical condition, the adjusted OR was 8.3 (95% CI, 1.0–65.3) for HAM/TSP and for

FIGURE 1. Frequency of HTLV-1 infection in offspring of seropositive mothers, according to the mothers' clinical condition, Peru



Notes:

Panel A. All offspring ($n = 370$). Offspring of mothers with strongyloidiasis *versus* offspring of asymptomatic mothers: $P = 0.01$ (chi-square test; continuity correction).

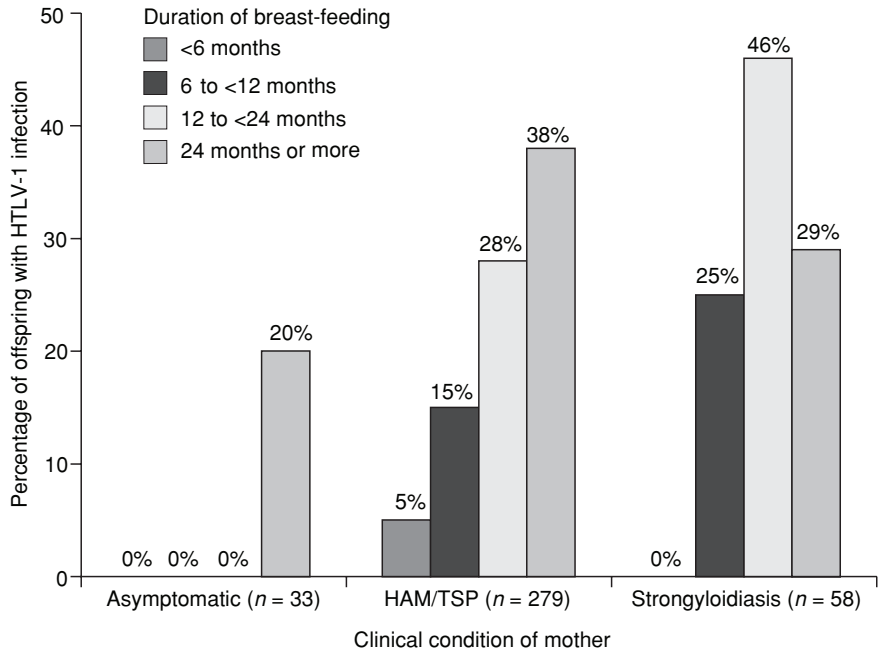
Panel B. Only children who had not received a blood transfusion and who were less than 13 years old when they were tested for HTLV-1 ($n = 58$). Children of mothers with HAM/TSP *versus* children of asymptomatic mothers: $P = 0.04$ (Fisher's exact test). Children of mothers with strongyloidiasis *versus* children of asymptomatic mothers: $P = 0.02$ (Fisher's exact test).

TABLE 2. Bivariate and multivariate comparison of HTLV-1–positive and HTLV-1–negative offspring of HTLV-1–positive mothers, Peru

Characteristic	HTLV-1–positive offspring (n = 72)	HTLV-1–negative offspring (n = 298)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)[a]
Female sex	49 (68%)	165 (55%)	1.7 (1.0–3.0)	1.8 (1.0–3.3)
Mean age at time of HTLV-1 test, years (SD)	25.5 (12.0)	25.7 (12.1)	1.0 (1.0–1.0)[b]	1.0 (1.0–1.0)[b]
Breast-feeding:[c]				
< 6 months	3 (4%)	78 (28%)	1	1
6 to < 12 months	12 (18%)	69 (25%)	4.5 (1.2–6.7)	5.7 (1.5–22.2)
12 to < 24 months	42 (62%)	106 (39%)	10.3 (3.1–34.5)	15.1 (4.2–54.1)
≥ 24 months	11 (16%)	22 (8%)	13.0 (3.3–50.7)	18.8 (4.4–79.8)
Vaginal delivery	66 (96%)	258 (94%)	1.5 (0.4–5.1)	NA
Transfusion history	11 (16%)	15 (5%)	3.1 (1.4–7.0)	5.5 (2.0–15.2)
Mean age of mother at birth of child: years (SD)	27.3 (6.5)	26.7 (6.9)	1.0 (1.0–1.1)[b]	NA
First contact with mother:[d]				
1989–1993	1 (1%)	15 (5%)	1	1
1994–1998	39 (54%)	132 (44%)	4.4 (0.6–34.6)	5.0 (0.5–46.5)
1999–2003	32 (44%)	151 (51%)	3.2 (0.4–24.9)	3.4 (0.4–32.2)
Ethnic background of mother:				
Andean	56 (78%)	181 (62%)	2.1 (1.2–3.9)	NA
Condition of mother:				
Asymptomatic carrier	2 (3%)	31 (10%)	1	1
HAM/TSP	52 (72%)	227 (76%)	3.6 (0.8–15.3)	8.3 (1.0–65.3)
Strongyloidiasis	18 (25%)	40 (13%)	7.0 (1.5–32.4)	11.5 (1.4–98.4)

Note: CI: confidence interval; SD: standard deviation; NA: not applicable; HAM/TSP: HTLV-1–associated myelopathy/tropical spastic paraparesis.
[a] Multiple logistic regression. The final model (Nagelkerke R square: 0.25) included: age at the time of HTLV-1 testing, duration of breast-feeding, transfusion history, sex, clinical condition of the mother, and first contact with the mother.
[b] Odds ratio expressed per unit of increase in the independent variable.
[c] Data on breast-feeding duration were available for 343 of 370 subjects.
[d] Year of first consultation and of HTLV-1 testing of the mothers at the study center.

FIGURE 2. Frequency of HTLV-1 infection in offspring of seropositive mothers according to the mothers' clinical condition and the duration of breast-feeding, Peru



strongyloidiasis the adjusted OR was 11.5 (95% CI 1.4–98.4) in comparison with offspring of asymptomatic mothers. For blood transfusion, the adjusted OR was 5.5 (95% CI 2.0–15.2). The effect of Andean ethnic origin disappeared when duration of breast-feeding was entered in the model.

DISCUSSION

We found higher proportions of HTLV-1 infection among offspring of mothers with strongyloidiasis or HAM/TSP than in offspring of asymptomatic mothers. Duration of breast-feeding and history of blood transfusion were also associated with HTLV-1 seropositivity among the offspring of infected mothers.

Since many of the study subjects were of adult age when they were tested, they could have been exposed

to HTLV-1 through sexual contact. However, the inclusion of age at the time of HTLV-1 testing in the multiple logistic regression analysis did not alter the results. In addition, we did not find associations between sexual risk behavior or drug use and HTLV-1 infection. In spite of these arguments, the possibility of horizontal transmission cannot be ruled out completely.

Blood transfusion is another possible mode of transmission (5). An association between transfusion history and HTLV-1 infection has been reported in several prevalence studies (13, 24). HTLV-1 screening of blood donors was introduced in Peru in 1998 (15, 16). In this study, most transfusions had occurred before that date and could therefore be the source of HTLV-1 infection in some of the 11 seropositive subjects with a transfusion history. On the other hand, 10 of these subjects were also breast-fed; 7 of 9 subjects who had siblings tested had at least one HTLV-1–positive sibling.

Ninety-seven percent of the study subjects had been breast-fed and as many as 79% of them were breast-fed for more than 6 months. This reflects the frequent practice of extended breast-feeding in Peru: up to 95% of Peruvian infants are breast-fed and nearly 50% continue to breast-feed during their second year of life (25). Consistent with other reports, we found a strong association and a significant trend between duration of breast-feeding and HTLV-1 infection (9, 10, 26). In this study, Andean ethnic background was associated with mother-to-child transmission on bivariate but not on multivariate analysis, probably because of the strong link between ethnic background and duration of breast-feeding.

Because it was not possible to establish with certainty the cause of HTLV-1 infection in the whole population, we described a subgroup of children under 13 years old who had not received a blood transfusion, in whom we considered mother-to-child transmission to be the only possible route of infection. Previous surveys have shown that after breast-feeding, no horizontal or casual transmission of HTLV-1 occurs prior to puberty (2). The association between HTLV-1 infection in the children and the clinical condition of the mother was also present in this subgroup. These findings differ from a study in Colombia in which no differences in transmission were found between HAM/TSP patients and asymptomatic carriers (27).

The diagnoses of HAM/TSP and strongyloidiasis were made after the children were born. Rather than indicating a direct relationship between these diseases and mother-to-child transmission of HTLV-1, our findings suggest that the same women who transmit the infection to their children are also more likely to develop HAM/TSP or strongyloidiasis, possibly later in life.

One hypothesis that could explain these findings is that women with high HTLV-1 provirus loads could be at increased risk for both transmitting the virus and developing HTLV-1–associated diseases. The HTLV-1 provirus load remains stable over time in infected individuals but this equilibrium set point of the provirus load can vary considerably between individuals (28). The risk of mother-to-child transmission depends on the provirus load in breast milk, which correlates well with the provirus load in peripheral blood mononuclear cells (PBMC) (11). Several studies have shown increased provirus loads in PBMC of HAM/TSP patients (29, 30) and of patients with HTLV-1 and strongyloidiasis (31). In this study, the proportion of infection was higher among the offspring of mothers with strongyloidiasis (31%) than among those of mothers with HAM/TSP (19%), although this difference was not statistically significant. It is unclear whether variations in provirus load could account for this difference. An alternative explanation could be a similar genetic background of mothers and children, determining on one hand increased susceptibility to HTLV-1 infection (32), and on the other hand to the development of HAM/TSP and particularly of strongyloidiasis (33).

In our study population, the frequency of HTLV-1 infection was higher among female offspring, although this difference was not statistically significant. Predominance of women infected with HTLV-1 has been recognized regularly in epidemiological studies among healthy adults (34, 35). Considering that the female-to-male ratio of HTLV-1 infection increases with age, this predominance has been attributed to male-to-female sexual transmission (35). On the other hand, some authors have suggested that girls could also be more susceptible to mother-to-child transmission than boys (10). Our data are consistent with the latter hypothesis, because in the subgroup of children who had been tested before they were 13 years old and who had never received a blood transfusion, the frequency of infection tended to be higher among girls (10 out of 34 girls were infected *versus* 3 out of 24 boys).

In this retrospective study, it is impossible to establish with certainty the temporal relationships between HTLV-1 infection and development of strongyloidiasis or HAM/TSP among the mothers, and transmission of HTLV-1 to their children. However, careful analysis of retrospective data is the only epidemiological tool we have to improve our understanding of HTLV-1 transmission, because prospective and controlled research would be impossible from an ethical point of view.

The limited number of offspring of mothers with asymptomatic HTLV-1 infection is another limitation of this study. Asymptomatic mothers were recruited mainly in the last years of the study period, after being diagnosed with HTLV infection through blood bank screening (22 out of 26 asymptomatic mothers). In addition, the number of offspring tested was lower in this group (1.3 per mother) than for mothers with HAM/TSP and strongyloidiasis (2.7 and 2.6 children per mother, respectively). Asymptomatic mothers were probably less motivated to bring their offspring to the study center for testing than were the mothers with HTLV-1–associated diseases. Although this limitation has affected the strength of this study, we do not think that it altered the main findings.

As part of HTLV-1 counseling for women, we recommend that they bottle-feed their children unless they have no regular access to clean water, in which case a reasonable alternative would be to breast-feed for no longer than six months. In southern Japan, screening pregnant women and limiting breast-feeding have proven to effectively reduce the prevalence of HTLV-1 in the general population (36).

In conclusion, not only duration of breast-feeding and transfusion history, but also maternal HAM/TSP and particularly strongyloidiasis were found to be associated with seropositivity among offspring of HTLV-1–infected mothers. Better knowledge of the mechanisms of mother-to-child transmission is crucial for improving HTLV-1 prevention strategies in endemic areas, particularly where HTLV-1 screening is limited and where replacement feeding of infants may be harmful due to poor water quality and limited access to formula feeding.

Acknowledgements. This work was supported in part by the Minority International Research Training (MIRT) Program through the University of Alabama at Birmingham, from the Fogarty International Center, National Institutes of Health, U.S.A., and the Directorate-General for Development Cooperation (DGDC) of the Belgian Government through a Framework Agreement with the Institute of Tropical Medicine of Antwerp. We wish to thank Ward Schrooten for his support with statistical analysis, and the health workers Afilio Tello and Juana Huerta for their care of HTLV-1–infected people.

REFERENCES

1. Poiesz BJ, Ruscetti FW, Gadzar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T cell lymphoma. Proc Natl Acad Sci USA. 1980;77(12):7415–9.
2. Ando Y, Matsumoto Y, Nakano S, Saito K, Kakimoto K, Tanigawa T, et al. Long-term follow up study of vertical HTLV-I infection in children breast-fed by seropositive mothers. J Infect. 2003;46(3):177–9.
3. Fujino T, Nagata Y. HTLV-I transmission from mother to child. J Reprod Immunol. 2000;47(2):197–206.
4. Roucoux DF, Wang B, Smith D, Nass CC, Smith J, Hutching ST, et al. A prospective study of sexual transmission of human T lymphotropic virus (HTLV)-I and HTLV-II. J Infect Dis. 2005;191(9):1490–7.
5. Okochi K, Sato H, Hinuma Y. A retrospective study on transmission of adult T cell leukemia virus by blood transfusion: seroconversion in recipients. Vox Sang. 1984;46(5): 245–53.
6. Lee HH, Weiss SH, Brown LS, Mildvan D, Shorty V, Saravolatz L, et al. Patterns of HIV-1 and HTLV-I/II in intravenous drug abusers from the middle atlantic and central regions of the USA. J Infect Dis. 1990;162(2):347–52.
7. Blattner WA. Epidemiology of HTLV-I and associated diseases. In: Blattner WA, ed. Human retrovirology: HTLV. New York: Raven Press; 1990.
8. Bittencourt AL, Sabino EC, Costa MC, Pedroso C, Moreira L. No evidence of vertical transmission of HTLV-I in bottle-fed children. Rev Inst Med Trop Sao Paulo. 2002;44(2):63–5.
9. Wiktor SZ, Pate EJ, Rosenberg PS, Barnett M, Palmer P, Medeiros D, et al. Mother-to-child transmission of human T-cell lymphotropic virus type I associated with prolonged breast-feeding. J Hum Virol. 1997;1(1):37–44.
10. Ureta-Vidal A, Angelin-Duclos C, Tortevoye P, Murphy E, Lepere JF, Buigues RP, et al. Mother-to-child transmission of human T-cell-leukemia/lymphoma virus type I: implication of high antiviral antibody titer and high proviral load in carrier mothers. Int J Cancer. 1999;82(6):832–6.
11. Li HC, Biggar RJ, Miley WJ, Maloney EM, Cranston B, Hanchard B, et al. Provirus load in breast milk and risk of mother-to-child transmission of human T lymphotropic virus type I. J Infect Dis. 2004;190(7):1275–8.
12. Biggar RJ, Ng J, Kim N, Hisada M, Li HC, Cranston B, et al. Human leukocyte antigen concordance and the transmission risk via breast-feeding of human T cell lymphotropic virus type I. J Infect Dis 2006;193(2):277–82.
13. Sanchez-Palacios C, Gotuzzo E, Vandamme AM, Maldonado Y. Seroprevalence and risk factors for human T-cell lymphotropic virus (HTLV-I) infection among ethnically and geographically diverse Peruvian women. Int J Infect Dis. 2003;7(2):132–7.
14. Alarcon JO, Friedman HB, Montano SM, Zunt JR, Holmes KK, Quinnan GV Jr. High endemicity of human T-cell lymphotropic virus type 1 among pregnant women in Peru. J Acquir Immune Defic Syndr. 2006;42(5):604–9.
15. Fuentes J, Roca O. Peru's experience with a national blood banking program. Rev Panam Salud Publica. 2003;13(2–3):165–71.
16. Gotuzzo E. Risk of transfusion-transmitted human T-cell lymphotropic virus-type I in Latin America. Int J Infect Dis. 2000;4(2): 59–61.
17. Gotuzzo E, Cabrera J, Deza J, Verdonck K, Vandamme AM, Cairampoma R, et al. Clinical characteristics of patients in Peru with human T cell lymphotropic virus type 1-associated tropical spastic paraparesis. Clin Infect Dis. 2004;39(7):939–44.
18. Araujo A, Hall WW. Human T-lymphotropic virus type II and neurological disease. Ann Neurol. 2004;56(1):10–9.
19. Zunt JR, La Rosa AM, Peinado J, Lama JR, Suarez L, Pun M, et al. Risk factors for HTLV-II infection in Peruvian men who have sex with men. Am J Trop Med Hyg 2006;74(5): 922–5.
20. Terashima A, Alvarez H, Tello R, Infante R, Freedman DO, Gotuzzo E. Treatment failure in intestinal strongyloidiasis: an indicator of HTLV-1 infection. Int J Infect Dis. 2002;6(1): 28–30.
21. Gotuzzo E, Terashima A, Alvarez H, Tello R, Infante R, Watts DM, et al. Strongyloides stercoralis hyperinfection associated with human T cell lymphotropic virus type-1 infection in Peru. Am J Trop Med Hyg. 1999;60(1): 146–9.
22. Hirata T, Uchima N, Kishimoto K, Zaha O, Kinjo N, Hokama A, et al. Impairment of host immune response against Strongyloides stercoralis by human T cell lymphotropic virus type 1 infection. Am J Trop Med Hyg. 2006;74(2):246–9.
23. World Health Organization (WHO). Report of the scientific group on HTLV-I infections and associated diseases (Kagoshima, Japan, 10–15 December 1988). Manila: WHO; 1989. Pp 17–8.
24. Schreiber GB, Murphy EL, Horton JA, Wright DJ, Garfein R, Chien HC, et al. Risk factors for human T-cell lymphotropic virus types I and II (HTLV-I and -II) in blood donors: the Retrovirus Epidemiology Donor Study. NHLBI Retrovirus Epidemiology Donor Study. J Acquir Immune Defic Syndr Hum Retrovirol. 1997;14(3):263–71.
25. Rice S, Coombs D, Fish L, Leeper J. Breast-feeding and contraception in Peru. J Health Popul Nutr. 2002;20(1):51–8.
26. Hisada M, Maloney EM, Sawada T, Miley WJ, Palmer P, Hanchard B, et al. Virus markers associated with vertical transmission of human T lymphotropic virus type 1 in Jamaica. Clin Infect Dis. 2002;34(12):1551–7.
27. Arango C, Rugeles MT, Concha M, Borrero II, Lai H, Lai S, et al. Risk factors for HTLV-I mother-to-child transmission: influence of genetic markers. Braz J Infect Dis. 1998;2(3): 135–42.

28. Kubota R, Fujiyoshi T, Izumo S, Yashiki S, Maruyama I, Osame M, Sonoda, S. Fluctuation of HTLV-I proviral DNA in peripheral blood mononuclear cells of HTLV-I-associated myelopathy. J Neuroimmunol. 1993;42(2): 147–54.
29. Nagai M, Usuku K, Matsumoto W, Kodama D, Takenouchi N, Moritoyo T, et al. Analysis of HTLV-I proviral load in 202 HAM/TSP patients and 243 asymptomatic HTLV-I carriers: high proviral load strongly predisposes to HAM/TSP. J Neurovirol. 1998;4(6):586–93.
30. Montanheiro PA, Oliveira AC, Posada-Vergara MP, Milagres AC, Tauil C, Marchiori PE, et al. Human T-cell lymphotropic virus type I (HTLV-I) proviral DNA viral load among asymptomatic patients and patients with HTLV-I-associated myelopathy/tropical spastic paraparesis. Braz J Med Biol Res. 2005; 38(11): 1643–1647.
31. Gabet AS, Mortreux F, Talarmin A, Plumelle Y, Leclercq I, Leroy A, et al. High circulating proviral load with oligoclonal expansion of HTLV-1 bearing cells in HTLV-1 carriers with strongyloidiasis. Oncogene 2000;19(43): 4954–60.
32. Plancoulaine S, Gessain A, Joubert M, Tortevoye P, Jeanne I, Taralmin A, et al. Detection of a major gene predisposing to human T lymphotropic virus type I infection in children among an endemic population of African origin. J Infect Dis. 2000;182(2): 405–12.
33. Jeffery KJ, Siddiqui AA, Bunce M, Lloyd AL, Vine AM, Witkover AD, et al. The influence of HLA class I alleles and heterozygosity on the outcome of human T cell lymphotropic virus type I infection. J Immunol 2000; 165: 7278–84.
34. Rouet F, Meertens L, Courouble G, Herrmann-Storck C, Pabingui R, Chancerel B, et al. Serological, epidemiological, and molecular differences between human T-cell lymphotropic virus Type 1 (HTLV-1)-seropositive healthy carriers and persons with HTLV-I Gag indeterminate Western blot patterns from the Caribbean. J Clin Microbiol. 2001;39(4):1247–53.
35. Proietti FA, Carneiro-Proietti AB, Catalan-Soares BC, Murphy EL. Global epidemiology of HTLV-I infection and associated diseases. Oncogene. 2005; 24(39):6058–68.
36. Kashiwagi K, Furusyo N, Nakashima H, Kubo N, Kinukawa N, Hayashi J. A decrease in mother-to-child transmission of human T lymphotropic virus type I (HTLV-I) in Okinawa, Japan. Am J Trop Med Hyg. 2004:70(2): 158–63.

Manuscript received 5 September 2006. Revised version accepted for publication 20 September 2007.

RESUMEN

Infección frecuente por HTLV-1 en los hijos de mujeres peruanas con mielopatía/paraparesia espástica tropical asociada con el HTLV-1 o con estrongiloidiasis

Objetivos. Describir la frecuencia de la infección por HTLV-1 en los hijos e hijas de madres diagnosticadas con mielopatía/paraparesia espástica tropical asociada con el HTLV-1 (M/PET-HTLV-1), estrongiloidiasis o infección asintomática por HTLV-1, e identificar los factores asociados con la infección por HTLV-1.

Métodos. Para este estudio descriptivo se revisaron los registros de mujeres positivas a HTLV-1 y de sus hijos evaluados con pruebas para la infección por HTLV en un hospital público de Lima, Perú, entre 1989 y 2003. Eran elegibles para este estudio los hijos y las hijas de las mujeres que se presentaron con estrongiloidiasis, M/PET-HTLV-1 o infección asintomática.

Resultados. En el estudio participaron 370 personas: 279 hijos de 104 madres con M/PET-HTLV-1, 58 hijos de 22 madres con estrongiloidiasis y 33 hijos de 26 madres asintomáticas. La edad promedio de los participantes en el momento de su prueba para HTLV era de 26 años (desviación estándar: 12 años). De las personas estudiadas, 19% resultaron positivas a la infección por HTLV-1: 6% (2/33) de los hijos de madres asintomáticas, 19% (52/279) de los hijos de madres con M/PET-HTLV-1 y 31% (18/58) de los hijos de madres con estrongiloidiasis. Según el análisis de regresión logística múltiple, tres factores se asociaron significativamente con la infección por HTLV-1: a) duración de la lactancia materna por 12–24 meses (razón de posibilidades [*odds ratio*, OR] = 15,1; intervalo de confianza de 95% [IC95%]: 4,2 a 54,1, frente a la lactancia materna por menos de 6 meses); b) que la madre presentara M/PET-HTLV-1 o estrongiloidiasis (OR = 8,3; IC95%: 1,0 a 65,3 y OR = 11,5; IC95%: 1,4 a 98,4, respectivamente, en comparación con los hijos de madres asintomáticas); y c) los antecedentes de haber recibido una transfusión sanguínea (OR = 5,5; IC95%: 2,0 a 15,2).

Conclusiones. Además de los factores de riesgo de la transmisión de la infección por HTLV-1 conocidos (duración de la lactancia materna y antecedentes de transfusión sanguínea), el diagnóstico materno de M/PET-HTLV-1 y el de estrongiloidiasis se asociaron significativamente con la infección por HTLV-1 en los hijos de madres seropositivas.

Palabras clave

Lactancia materna, transmisión vertical de enfermedades, virus 1 linfotrópico T humano, HTLV-1, paraparesis tropical espástica, transmisión de enfermedad, Strongyloides, Perú.