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Evidence for Sexual and Mother-to-Child Transmission of Human T Lymphotropic Virus Type II among Guaymi Indians, Panama

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Guaymi Indians, a non–intravenous drug–using population in which human T cell lymphotropic virus type II (HTLV-II) is endemic, were studied in Changuinola, Panama, to identify the prevalence and modes of transmission of HTLV-II. A population-based survey showed that 352 (9.5%) of the 3686 participants were seropositive for HTLV-II. Infection rates were the same for male and female subjects and increased significantly with age, beginning in young adulthood. HTLV-II infection status was highly concordant among spouses ($P < .001$) and between mother and child; of children aged 1–10 years, 36 of 219 born to seropositive mothers were seropositive compared with 3 of 997 born to seronegative mothers ($P < .001$). The strong associations of HTLV-II infection with age and with an infected spouse in adults and of infection in children with infection in their mothers strongly suggest sexual and mother-to-child transmission of HTLV-II in this population.

Human T lymphotropic virus types I and II (HTLV-I and -II) are closely related retroviruses. Unlike HTLV-I, HTLV-II has not yet been firmly associated with any disease, although recent reports have linked HTLV-II to neurologic and hematologic illness in small numbers of patients [1, 2]. Screening at US blood banks detects >1000 HTLV-infected donors a year, most of whom are infected with HTLV-II [3]. Relatively little information is available for counseling HTLV-II–infected donors about the routes of transmission [4].

Previous studies have documented HTLV-II seroprevalence rates of 8%–9% in small numbers of Guaymi Indians in Changuinola, Panama [5]. Established risk factors for HTLV-II infection, including intravenous drug use (IVDU) and blood transfusions, are extremely rare in this population. To identify modes of transmission of HTLV-II in this population, we determined their prevalence of HTLV-II infection, ascertained demographic risk factors, and analyzed patterns of clustering of infected persons.

Materials and Methods

Study population. The Guaymi Indians are an Amerindian tribe who inhabit isolated areas of western Panama and adjacent

Costa Rica. In the last several decades, large numbers of Guaymi have migrated to work on banana plantations (fincas) around Changuinola. The Guaymi households primarily consist of family units and unmarried male workers.

All Guaymi ≥1 year old living on the 15 fincas around Changuinola were potentially eligible for our study. Ten fincas were chosen on the basis of accessibility and cooperation from union representatives for a potential study population of ~4500 Guaymi. All eligible Guaymi living on the 10 fincas were approached for enrollment.

Data and specimen collection. Between January 1991 and May 1993, study teams visited each Guaymi household. Basic data, including name, age, sex, and family relationships, were obtained by interview of adults. Venous blood was obtained from each participant for serologic studies.

Laboratory methods. Serum specimens were screened for HTLV antibodies with both an HTLV-I whole-virus ELISA (HTLV-I EIA; Genetic Systems, Redmond, WA) and a recombinant HTLV-I envelope protein (p21e)–spiked whole virus ELISA (recombinant HTLV-I/II EIA; Cambridge Biotech, Worcester, MA). These tests detect antibodies to both HTLV-I and -II.

Specimens reactive in either ELISA were tested by a p21e-spiked HTLV-I Western blot assay (Cambridge Biotech). A specimen with reactivity to both *env*-encoded glycoprotein p21e and *gag*-encoded protein p24 was considered positive for HTLV-I/II antibody. A specimen was considered indeterminate if it showed reactivity to at least one viral protein on Western blot but did not meet the criteria for positivity. Indeterminate specimens were considered HTLV-negative in further analyses [6].

A subset of specimens positive for HTLV-I/II antibody were typed using an HTLV-I Western blot (Western Blot 2.3; Genelabs Diagnostics, Singapore) spiked with *env* p21e and the type-specific envelope glycoproteins MTA-1 and K-55. Antibody reactivity to MTA-1 and K-55 is specific for HTLV-I and -II infection, respectively [7]. A specimen was considered positive for HTLV-II if it showed reactivity to K-55.

Statistical methods. Data were analyzed using SAS version 6.08 software (SAS Institute, Cary, NC) and Epi Info 5.0 software (CDC). Univariate analyses were done with the χ^2 test and the χ^2 test for trend. Statistical testing was based on Fisher's exact test. Summary χ^2 statistics for stratified data were calculated using the Mantel-Haenszel method.

Results

HTLV seroprevalence. Of 4451 eligible Guaymi, 3636 (81.7%) were available and agreed to participate. Reasons for nonparticipation included refusal (506 persons), absence at the time of the study visits (189), and refusal because of prior HTLV-II testing in a separate hospital-based study (120) [8]. Of the latter 120, 57 persons were linked to test results and were considered additional participants. Seven samples were damaged, yielding 3686 total subjects (82.8%). Age group–specific participation rates exceeded 83%, except in the <5 years age group (62%).

Of 3686 Guaymi tested, 381 (10.3%) had at least one reactive ELISA screening result; 352 (9.5%) were confirmed seropositive for HTLV-I/II by Western blot. All 77 HTLV-I/II–positive specimens from the first two fincas surveyed were further tested by Western blot; 75 were typed as HTLV-II and 2 were untypeable. On the basis of these results, and those of previous studies, which found only HTLV-II in HTLV-infected Guaymi [9], we considered all HTLV-I/II–positive serologic tests to represent HTLV-II infection. Twenty-nine samples had indeterminate reactions on Western blot.

Figure 1 shows the seroprevalence of HTLV-II by sex and 5-year age group. Antibody was detected in subjects of all ages; however, a marked increase in seroprevalence was seen in both sexes beginning in adolescence and peaking in the fourth decade. A subsequent decrease in seroprevalence was seen in female subjects in the ≥45 years age group ($P = .05$).

HTLV-II seroprevalence rates increased at a younger age for female subjects. In the 15–19 years age group, the HTLV-II seroprevalence for females (7.0%) was higher than for males (1.6%, $P = .02$). For older groups, the seroprevalences were not significantly different. After adjustment for age, seroprevalences were similar for male (9.3%) and female subjects (9.2%, $P = .90$).

We also looked at HTLV-II seroprevalence as a function of marital status. Among women aged 15–20 years, the rate was higher for married women (19/189, 9.1%) than for unmarried women (2/67, 2.9%, $P = .15$), although this difference was not statistically significant. The rate among unmarried women was comparable to that among girls <15 years old (3.6%). The high rate of marriage in older women and the low rate in girls precluded similar comparisons. For married women, HTLV-II seroprevalence was higher among women with multiple marriages (28/111, 25.2%) than women with only one marriage (67/481, 13.9%), even after adjustment for age (Mantel-Haenszel, $P = .04$).

Seroprevalences for male subjects <20 years old were low (3.2%); only 10 men in this age group were married. Among men ≥20 years of age, rates for both married and unmarried men increased rapidly with age and were virtually indistinguishable. The overall HTLV-II seroprevalence for unmarried men (12.1%) was significantly higher than that for unmarried women (3.0%, $P < .001$).

Married couples. Analysis of the serologic status of married couples showed strong concordance between partners (table 1). Of 592 couples, 71 were concordantly seropositive (21 expected) and 439 concordantly seronegative (389 expected; $P < .001$). The seroprevalence among spouses of seropositive subjects was 46% compared with 12.6% ($P < .01$) among other adults in the same household and 16% for the adult Guaymi population overall.

There was an increasing trend in proportion of serologically positive concordant couples with age of either partner, reaching statistical significance when analyzed by age of the
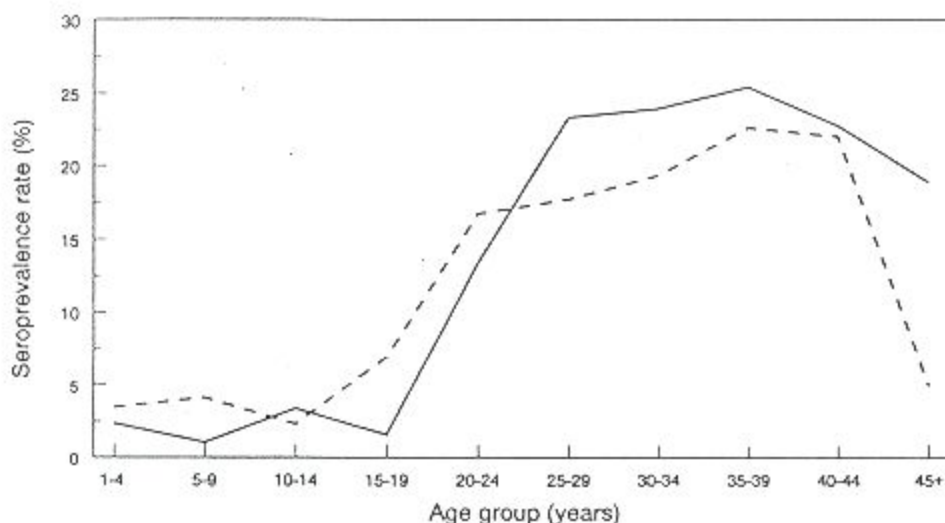
Figure 1. HTLV-II seroprevalence by 5-year age group and sex, Guaymi, Changuinola, 1991–1993. $P < .001$ for increasing seroprevalence with age in both males and females.

p<.001 for increasing seroprevalence
with age in both males and females

Agegroup	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45+	Total
Males	254	381	295	189	179	150	142	110	101	164	1965
Females	259	362	260	244	179	124	119	84	50	40	1721

female partner (Mantel-Haenszel, $P = .05$). No information about length of marriage or about other sex partners was obtained in the study, preventing analysis by these likely confounders. Among the serologically discordant couples, there were more couples with the male partner seropositive (58) than with the female partner seropositive (24). This imbalance was primarily found in discordant couples in which both partners had been married only once (40 couples with a seropositive man vs. 8 couples with a seropositive woman). The excess number of male-positive couples was found in all age groups (table 1).

Children and parents. Among children ⩽10 years of age, 36 (16.4%) of 219 children of seropositive mothers were seropositive compared with 3 (0.3%) of 997 children of seronegative mothers (relative risk [RR] = 65, $P < .001$). An association was observed between the serostatus of father and child

(RR = 7, $P < .001$); however, this association disappeared when controlled for maternal serostatus (data not shown).

Over the birth to 10 years range, there was no increase in seroprevalence with age among children of seropositive mothers (χ^2 for trend = 0.29, $P = .63$, data not shown).

Discussion

We confirmed the previously reported high HTLV-II seroprevalence among the Guaymi. These rates are the highest reported for non-IVDU populations. In addition, the large number of seropositive subjects in our study allowed detailed analyses of clustering not possible in earlier studies. Unlike previous studies, we found HTLV-II infection in subjects of all ages, although, as is also seen in HTLV-I–infected populations, infection is uncommon in preadolescents [10, 11]. However, several features of the HTLV-II seroprevalence

Table 1. HTLV-II serologic status of 592 married couples by age of wife.

Age of wife, years	M⁻F⁻	M⁻F⁺	M⁺F⁻	M⁺F⁺	Total
<20	103	3 (2)	15 (10)	6	127
20–29	167	11 (4)	28 (21)	28	234
30–39	124	9 (2)	10 (7)	28	171
>39	45	1 (0)	5 (2)	9	60
Total	439	24	58	71	592

NOTE. $P = .05$ for trend of increasing seropositively concordant couples with age. M = male, F = female, − = HTLV-II–seronegative, + = HTLV-II–seropositive. Nos. in parentheses are no. of couples for which this is first marriage for both partners.

patterns are distinct from HTLV-I seroprevalence patterns for populations in Japan and the Caribbean. The increase in HTLV-II seroprevalences for young adults is more rapid than the rate reported with HTLV-I. HTLV-II rates plateau for both sexes, whereas HTLV-I rates continue to rise with age, especially in women. The comparable male and female HTLV-II seroprevalences contrast sharply with higher HTLV-I seroprevalences for women in Japan and the Caribbean.

Although sexual transmission of HTLV-I has been well documented [11, 12], sexual transmission of HTLV-II has not been as firmly established. Studies of US blood donors have shown sexual contact with an IVDU to be a risk factor for HTLV-II infection [13]. However, our previous smaller study of the Guaymi did not find evidence for clustering of HTLV-II infections among sex partners [5].

We have shown that HTLV-II seroprevalences increase with age, beginning in adolescence. Couples are strongly concordant for HTLV-II serologic status, and rates of serologic concordance among couples increase with age. Among female subjects, marital status is a risk factor for HTLV-II infection. These data indicate that sexual transmission of HTLV-II is a major mode of transmission in this population.

In Japan, cross-sectional studies have shown evidence of more efficient male-to-female than female-to-male sexual transmission of HTLV-I, especially after menopause [10, 12]. Seroprevalence of HTLV-I is higher among women than among men, and male-positive female-negative couples are less common than male-negative female-positive couples. Longitudinal studies in Japan also support a higher efficiency of male-to-female transmission [12].

The younger age structure of the Guaymi population makes comparison of study results with the Japanese data difficult. Nevertheless, in our study, similar HTLV-II seroprevalences for male and female subjects support bidirectional sexual transmission. Although male-positive discordant couples were more common than female-positive discordant couples, this was seen only in first-marriage couples, suggesting that Guaymi men are more likely to be infected with HTLV-II at the time of their first marriage.

Unmarried men were more likely to be infected than unmarried women. Although sexual practices in unmarried men might account for this difference, no behavioral data were collected.

The strong association of infected children with infected mothers argues for mother-to-child transmission, while the evidence of stable seroprevalences for children 1–10 years old argues for no additional transmission before puberty. For HTLV-I, breast-feeding is the predominant means of mother-to-child transmission; ~25% of breast-fed infants of HTLV-I–infected mothers will become infected compared with only 5% of non–breast-fed infants [4]. As occurs with HTLV-I, HTLV-II–infected lymphocytes are present in breast milk of HTLV-II–infected mothers [14]. Breast-feed-

ing is almost universally practiced among the Guaymi, and the infection rate for children of HTLV-II–infected Guaymi mothers (16.5%) is comparable to that for breast-fed infants of HTLV-I–infected mothers. A recent study documented transmission of HTLV-II from a mother to her child, probably by breast-feeding [15].

The presence of 3 HTLV-II–seropositive children of HTLV-II–seronegative mothers is unexplained. Although wet nursing is uncommon among the Guaymi, it could account for an alternative source of infection. The lower seroprevalence of HTLV-II in the oldest women is also unexplained; a cohort effect due to recent migration could be responsible.

Although the strong serologic clustering within families in our study provides evidence for mother-to-child and sexual transmission, our study is limited by its cross-sectional design and the absence of any behavioral data. Further studies of laboratory and behavioral factors associated with HTLV-II infection among the Guaymi are in progress.

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Human Papillomavirus Infection Is Transient in Young Women: A Population-Based Cohort Study

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The prevalence of human papillomavirus (HPV) infection in cervical cell scrapes from a cohort of 276 young women was determined by a general two-step polymerase chain reaction. HPV infection fluctuated among young women during a 2-year interval. The total prevalence of HPV infection decreased from 21% to 8.3%. The most prevalent HPV types at enrollment were HPV-16 (3.3%) and HPV-6 (2.9%). At follow-up, the most common type was HPV-16 (2.9%), while no HPV-6 was detected. In 2 women only, the same HPV type persisted. Regression of HPV infection was found in 80% of the women. A new HPV type–specific infection was detected in 7.2% of the women and was independently associated with a new sex partner or an abnormal smear since enrollment.

So far, 67 different human papillomavirus (HPV) genotypes have been identified, of which 28 are from benign and malignant genital lesions [1]. The anogenital HPVs have been categorized as low risk (types 6, 11, 42, 43, 44), intermediate risk (types 31, 33, 35, 51, 52, 58), and high risk (types 16, 18, 45, 56) viruses on the basis of results from epidemiologic studies and data from the ability to transform human keratinocytes in vitro [2, 3].

Polymerase chain reaction (PCR)–based methods have revealed that the prevalence of HPV infection in cytologically normal women ranges from 3.5% to 53% [4, 5]. HPV DNA is present in 80%–100% of patients with high-grade cervical intraepithelial neoplasia (CIN). HPV-16 is the most frequently

detected type, but other HPV types are also closely related to cervical cancer. It is therefore of interest to follow the natural history of HPV infection in a population of women. We determined the prevalence of HPV infection in a population-based cohort of young women by using two-step PCR [4], a technique that has been proven to detect a broad spectrum of HPVs. By analyzing cervical scrapes from the women on two occasions 2 years apart, we aimed at evaluating the regression, acquisition, and persistence of HPV infection.

Materials and Methods

Study population. All women aged 19, 21, 23, and 25 who were inhabitants of a primary health care area in Umeå, according to public record, were invited by letter to participate in the enrollment study between September 1989 and August 1990. Of 816 eligible women, 205 declined the invitation. Of these 205 women, 135 were interviewed by telephone and gave their reason for not participating. Among these, 90 women had recently consulted a gynecologist, 23 had never had sexual intercourse, 18 were pregnant, and 4 could give no specific reason. The age, social background, and education of these nonattenders did not differ from the attending women. In addition, 70 women could not be reached at all, but as their ages were known, their age group distribution was analyzed and found not to differ from that of attending women.