

Clinical Manifestations Associated with HTLV Type I Infection: A Cross-Sectional Study

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ABSTRACT

Human T-lymphotropic virus type I (HTLV-I) causes HTLV-I-associated myelopathy/tropical spastic paraparesis and adult T cell leukemia in a small percentage of infected individuals. HTLV-I infection is increasingly associated with clinical manifestations. To determine the prevalence of clinical manifestations in HTLV-I infected individuals, we conducted a cross-sectional study of 115 HTLV-I-infected blood donors without myelopathy and 115 age- and sex-matched seronegative controls. Subjects answered a standardized questionnaire and underwent physical examination. Compared with controls, HTLV-I-infected subjects were more likely to report arm or leg weakness (OR = 3.8, 95% CI: 1.4–10.2; OR = 4.0, 95% CI: 1.6–9.8, respectively), hand or foot numbness (OR = 2.1, 95% CI: 1.1–3.9; OR = 4.8, 95% CI: 2.0–11.7, respectively), arthralgia (OR = 3.3, 95% CI: 1.7–6.4), nocturia (OR = 2.7, 95% CI: 1.04–6.8), erectile dysfunction (OR = 4.0, 95% CI: 1.6–9.8), and to have gingivitis (OR = 3.8, 95% CI: 1.8–7.9), periodontitis (OR = 10.0, 95% CI: 2.3–42.8), and dry oral mucosa (OR = 7.5, 95% CI: 1.7–32.8). HTLV-I infection is associated with a variety of clinical manifestations, which may occur in patients who have not developed myelopathy.

INTRODUCTION

HUMAN T-LYMPHOTROPIC VIRUS TYPE I (HTLV-I) was the first human retrovirus identified.¹ It is estimated that 15–20 million people live with HTLV-I infection worldwide. High prevalence rates are found in a few areas such as Japan, parts of West Africa, Caribbean Islands, and South America.² In Brazil, the highest prevalence is found in Salvador, the capital of the state of Bahia (1.76% in the overall population).³

HTLV-I is the causative agent of adult T cell leukemia/lymphoma (ATLL) and HTLV-I-associated myelopathy/tropical spastic paraparesis/ (HAM/TSP).^{4,5} Cases of ATLL and HAM/TSP can be found in all endemic areas, but prevalence and incidence rates vary substantially across geographic areas.² The vast majority of infected persons are thought to remain asymptomatic and only a small fraction of them develops ATLL or HAM/TSP. It is estimated that HTLV-I carriers have a < 2% risk of developing HAM/TSP and ~5% lifetime risk of developing ATLL when infected before the age of 20.⁶ HAM/TSP

is a debilitating illness of slow and progressive onset, characterized by spastic paraparesis. Although most HTLV-I-infected persons do not develop any complications, there are recent data showing an increased prevalence of erectile dysfunction, bladder function abnormalities, and peripheral neuropathy^{7,8} in HTLV-I carriers who do not fulfill the WHO diagnostic criteria of HAM/TSP.⁹ HTLV-I infection has also been linked to other clinical manifestations, but the spectrum of diseases caused by HTLV-I remains unclear. There is increasing evidence that HTLV-I infection might be associated with inflammatory conditions such as uveitis,¹⁰ Sjögren's syndrome,¹¹ polymyositis, lymphocytic alveolitis, and arthritis.^{2,12} It has also been associated with infectious complications¹³: infective dermatitis in children,¹⁴ increased carriage of *Strongyloides stercoralis* and high risk of disseminated strongyloidiasis,¹⁵ and increased incidence of bladder or kidney infection.¹² The causative role of HTLV-I infection is yet to be proven for most of these observations, which were mainly based on small case series.

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The natural history and pathological effects of HTLV-I infection remain poorly defined. HTLV-I carriers might develop early signs of myelopathy or other HTLV-I-associated illnesses and remain undiagnosed by the current diagnostic criteria, which can cause a delay in proper medical care and potentially miss a critical window for therapy.¹⁶ In an attempt to better describe the spectrum of complications associated with HTLV-I infection, we conducted a cross-sectional study of HTLV-I-infected and -uninfected blood donors in Salvador, Brazil. In this report, we performed a comprehensive evaluation and analysis of the association between HTLV-I infection and current complaints and findings on physical examination.

MATERIALS AND METHODS

Study site and population

The present study was performed in Salvador, the capital city of the state of Bahia, located on the Atlantic coast of Northeastern Brazil. Salvador has a population of approximately 2.5 million inhabitants, most of whom are of African or African/Portuguese descent, and is characterized by marked socioeconomic differences.¹⁷

Cases. We recruited cases for this study from the HTLV-I Multidisciplinary Clinic at the Hospital Universitário Prof. Edgard Santos in Salvador, which serves a diverse population of HTLV-I-infected patients, referred from blood banks and neurology and dermatology clinics in the city. The HTLV-I Clinic provided care to approximately 250 HTLV-I-infected patients from May 2004 to July 2005. We selected cases from the patients enrolled in the clinic who were blood donors originally referred from three major blood banks in the city, after attempted blood donation and diagnosis of HTLV-I infection by ELISA (Cambridge Biotech Corp., Worcester, MA). Before enrollment in the clinic, HTLV-I diagnosis was confirmed by Western Blot analysis (HTLV blot 2.4, Genelab, Singapore). In Brazil, blood donors are volunteers who do not receive any monetary incentive from donating blood.

Cases were defined as subjects with HTLV-I infection who did not have a diagnosis of HAM/TSP. Two neurological scales were used to characterize the neurological abnormalities: Expanded Disability Status Scale (EDSS)¹⁸ and Osame's Motor Disability Score (OMDS).¹⁹ According to the World Health Organization HAM/TSP is clinically defined as an EDSS of ≥ 2 and/or an Osame score of ≥ 1 . Patients meeting either criterion were excluded from the study.

Controls. A group of matched controls was recruited from one of three major blood banks in Salvador (STS) at the time of blood donation. Controls were blood donors who were not infected with HTLV-1. We selected one control per case from our sample group of recruited controls, matching by age (± 5 years) and sex.

We excluded from the study subjects who were < 18 or > 65 years of age, or who had a history of diabetes mellitus or a serologic diagnosis of HIV or HCV infection. The study was reviewed and approved by the Institutional Review Boards of the Hospital Universitário Prof. Edgard Santos and the Weill

Medical College of Cornell University. Informed consent was obtained from all subjects enrolled in the study.

Evaluations

To assess the frequency of symptoms, cases responded to a standardized questionnaire during a clinic visit and controls answered the same questionnaire at the time of blood donation. Demographic characteristics included income as a multiple of the minimum wage, which currently is equivalent to US\$ 167.00 per month. The frequencies of urinary, neurological, rheumatological, dental, ocular, and respiratory symptoms as well as the frequency of erectile dysfunction (ED) were assessed. Urinary frequency was defined as more than six micturitions/day and nocturia as getting up two or more times to urinate during the night. Urgency was considered as a sudden desire to void and dysuria as painful urination or burning sensation during urination. The five-item version of the International Index of Erectile Function (IIEF-5), which is a validated questionnaire, was used to assess the presence of ED. It consists of questions regarding problems with sex drive, erections, and ejaculation as well as overall satisfaction with sex life.²⁰ Weakness, paresthesia, difficulty walking or running, and arthralgia were considered current complaints if they occurred in the last 12 months and lasted for more than 1 week. Subjects were also questioned about current or past complaints of dry mouth and eyes, gingival bleeding, photophobia and blurry vision, shortness of breath, and cough.

All subjects underwent dental and neurological examinations as well as evaluation of joints for the presence of signs of inflammation. Cases were evaluated at the HTLV-I clinic by one of three neurologists and by a dentist. Controls were evaluated at the blood bank by an internist (M.F.C.) who was trained in the application of the neurological scales by a study neurologist and in the dental examination by the study dentist. The neurological and dental examinations were standardized among different examiners, and there was concordance of findings in a subset of subjects evaluated by the internist and neurologist and the internist and dentist. The neurological assessment was composed of an evaluation of strength in all four limbs, deep tendon reflexes, plantar reflexes (Babinski sign), and sensation (vibration, light touch, and pinprick). The EDSS and Osame (OMDS) scales were used to grade the findings. Spasticity was assessed by the modified Ashworth scale.²¹ The dental examination consisted of assessment of gingival membranes for the presence of bleeding, erythema, and edema (the presence of one or more of these signs defined gingivitis), evaluation of the presence of dental mobility, which is a marker of periodontitis, and of signs suggestive of dry oral mucosa.

Statistical analysis

Matched univariate odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by conditional logistic regression using Stata 7 software (Stata Corporation, College Station, TX) for all variables analyzed. Multiple conditional logistic regression was used to adjust for potential confounding variables. A p value < 0.05 was considered significant for statistical tests. No adjustment was made for multiple comparisons.

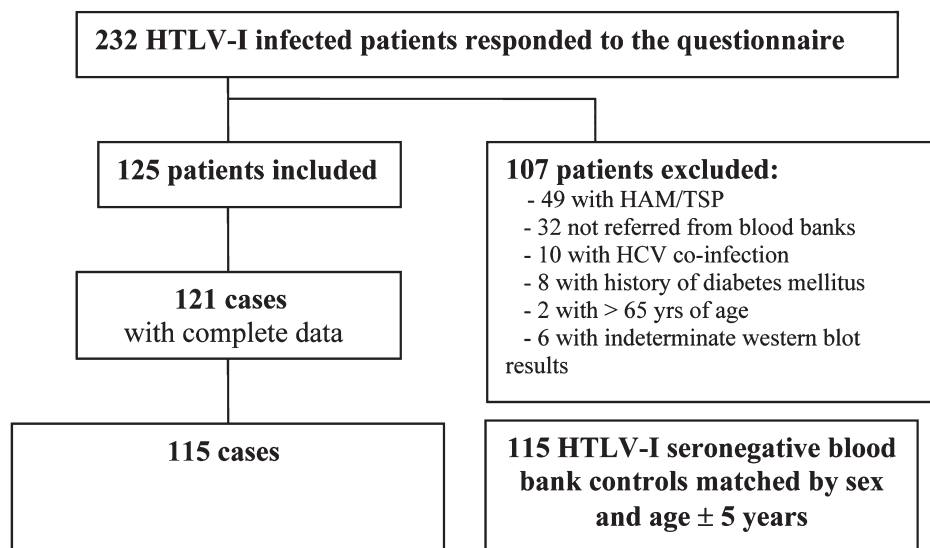


FIG. 1. Selection of study subjects.

RESULTS

Of the 232 HTLV-I-infected patients who attended the HTLV-I clinic and answered the questionnaire, 125 met the inclusion and exclusion criteria and were included in the study. Of the 125 subjects initially included, 2 did not complete or have the neurological examination and 2 had missing results of the Western blot analysis and were excluded from the analysis. We were not able to recruit controls to match 6 cases of extreme age, thus leaving 115 cases of HTLV-I-infected blood donors and 115 controls of HTLV-I-uninfected blood donors (Fig. 1).

Table 1 summarizes the demographic characteristics of the case and control subjects. Sixty-six of the 115 subjects included in each group were male. Despite matching, the mean age of

cases was slightly higher than controls. The case group was more likely to have a lower level of both education and income and to be mulatto or black. When these variables were analyzed as possible confounders, income level showed the strongest independent association with HTLV status ($p < 0.001$). Consequently, all analyses were adjusted for income level.

Table 2 summarizes the frequency of various symptoms. Compared to controls, HTLV-I-infected subjects were more likely to report complaints of hand and foot numbness [matched odds ratio (OR) = 2.1, 95% confidence interval (CI): 1.1–3.9; $p = 0.025$ and OR = 4.8, 95% CI: 2.0–11.7; $p < 0.001$, respectively], arm and leg weakness (OR = 3.8, 95% CI: 1.4–10.2; $p = 0.008$ and OR = 4.0, 95% CI: 1.6–9.8; $p = 0.002$, respectively), nocturia (OR = 2.7, 95% CI: 1.04–6.8; $p = 0.04$), arthralgia (OR = 3.3, 95% CI: 1.7–6.4; $p < 0.001$),

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF HTLV-1-INFECTED CASES AND MATCHED CONTROLS

	Case	Control	Matched OR ^a	95% CI	p
<i>N</i>	115	115			
Sex					
Male (%)	66 (57.4%)	66 (57.4%)			
Age, years, mean (SD)	45.2 (10.6)	41.7 (10.9)			
Race (%)					
White	22 (20.5%)	42 (37.1%)			
Mulatto	44 (41.1%)	40 (35.4%)	2.1	1.01–4.3	0.046
Black	39 (36.4%)	20 (17.7%)	3.9	1.7–9.2	0.002
Other	2 (1.8%)	11 (9.73)	0.3	0.1–1.5	0.143
Education (%)					
≤8 years	55 (48.2%)	29 (25.2%)	0.4	0.2–0.7	0.001
>8 years	59 (51.75%)	86 (74.7%)			
Income (%)					
≤4 × minimum wage ^b	91 (79.1%)	50 (43.4%)	0.14	0.06–0.03	<0.001
>4 × minimum wage	24 (20.8%)	65 (56.2%)			

^aConditional logistic regression.

^bMinimum wage is equivalent to US\$167.00 per month.

TABLE 2. UNIVARIATE AND MULTIVARIATE ANALYSES OF SYMPTOMS REPORTED BY HTLV-I-INFECTED SUBJECTS AND MATCHED CONTROLS

Symptoms	Case	Control	Matched OR ^a	95% CI	p	Adjusted OR ^{a,b}	95% CI	p
Neurological								
Hand numbness	36 (31.5%)	21 (18.2%)	2.1	1.1–3.9	0.025	2.2	1.0–4.6	0.037
Foot numbness	34 (29.5%)	11 (9.5%)	4.8	2.0–11.7	0.001	5.4	1.9–14.8	0.001
Arm weakness	19 (16.5%)	5 (4.3%)	3.8	1.4–10.2	0.008	3.7	1.2–11.2	0.02
Leg weakness	24 (20.8%)	6 (5.2%)	4.0	1.6–9.8	0.002	3.6	1.3–9.3	0.009
Difficulty walking	13 (11.3%)	0	—	—	—	—	—	—
Difficulty running	10 (8.7%)	10 (8.7%)	1.0	0.4–2.7	1.0	0.8	0.2–2.5	0.65
Urological								
Frequency	13 (11.4%)	19 (16.5%)	0.7	0.3–1.4	0.27	0.8	0.3–1.9	0.62
Nocturia	17 (14.7%)	7 (6.1%)	2.7	1.04–6.8	0.04	1.4	0.5–3.9	0.52
Urgency	10 (8.7%)	5 (4.3%)	2.3	0.7–7.3	0.17	1.7	0.5–6.4	0.40
Incontinence	9 (7.8%)	2 (1.7%)	4.5	0.97–20.2	0.054	3.4	0.6–19	0.16
Straining	8 (6.9%)	6 (5.2%)	1.3	0.4–3.8	0.59	1.9	0.6–6.6	0.29
Dysuria	11 (9.5%)	5 (4.3%)	2.5	0.8–8.0	0.12	3.0	0.8–11.9	0.10
Rheumatological								
Arthralgia	57 (49.5%)	29 (25.2%)	3.3	1.7–6.4	<0.001	3.4	1.6–7.0	0.001
Dental								
Xerostomia	24 (20.8%)	13 (11.3%)	1.9	0.95–3.9	0.068	1.5	0.7–3.4	0.32
Gingival bleeding	39 (34.2%)	25 (21.7%)	1.8	1.02–3.4	0.042	2.4	1.1–5.0	0.02
Ocular								
Dry eyes	31 (27.6%)	36 (31.3%)	0.8	0.4–1.5	0.41	0.4	0.2–1.0	0.051
Painful eyes	26 (23%)	20 (17.3%)	1.3	0.7–2.5	0.35	1.2	0.6–2.5	0.58
Respiratory								
Shortness of breath	20 (17.5%)	13 (11.3%)	1.6	0.8–3.5	0.19	1.3	0.5–2.9	0.59
Cough	18 (15.7%)	23 (20%)	0.7	0.4–1.5	0.38	0.8	0.3–1.8	0.57
Sexual function								
Erectile dysfunction	(<i>n</i> = 65) 24 (43%)	(<i>n</i> = 66) 11 (16.6%)	4.0	1.6–9.8	0.002	9.3	2.1–42.0	0.004

^aConditional logistic regression.

^bAfter adjustment for income level.

gingival bleeding (OR = 1.8, 95% CI: 1.02–3.4; *p* = 0.04), and erectile dysfunction (OR = 4.0, 95% CI: 1.6–9.8; *p* = 0.002). There was also a trend toward an association of incontinence and HTLV-I infection (OR = 4.5, 95% CI: 0.97–20.2; *p* = 0.054). In multivariate analysis, when data were adjusted for income level, HTLV-I-infected subjects remained more likely to report nocturia (OR = 1.4, 95% CI: 0.5–3.9) and incontinence (OR = 3.4, 95% CI: 0.6–19) but these differences were not statistically significant (*p* = 0.52 and *p* = 0.16, respectively). All other associations remained statistically significant after adjustment for income level.

Preliminary studies at our clinic and elsewhere showed evidence of urinary manifestations in a group of HTLV-I carriers.^{8,12} To determine if subjects with urological symptoms were more likely to report other types of symptoms, we grouped all other symptoms into six categories (neurological, rheumatologic, oral, ocular, respiratory, and sexual) and evaluated the percentage of subjects, stratified by HTLV-I serostatus, who re-

ported one or more symptom in each category (Table 3). Among HTLV-I-infected subjects, there was a statistically significant association between urological and neurological symptoms (*p* = 0.01) and a borderline association between urological symptoms and oral findings (*p* = 0.05). In contrast, HTLV-I-negative subjects who reported urinary symptoms were not more likely to report symptoms in any other category compared with those not reporting urinary symptoms.

Table 4 summarizes the findings on physical examination. HTLV-I infection was associated with presence of gingivitis (OR = 3.8, 95% CI: 1.8–7.9; *p* < 0.001), periodontitis (OR = 10.0, 95% CI: 2.3–42.8; *p* < 0.002), and dry oral mucosa (OR = 7.5, 95% CI: 1.7–32.8; *p* = 0.007); these differences remained significant after adjustment for income level. Although HTLV-I-infected subjects were more likely to report subjective neurological findings, the neurological examination failed to show significant differences between HTLV-I-infected subjects and seronegative controls. Both groups were evaluated us-

TABLE 3. ASSOCIATION OF URINARY SYMPTOMS WITH OTHER CATEGORIES OF SYMPTOMS IN HTLV-I-INFECTED SUBJECTS AND MATCHED CONTROLS

	Case					Controls				
	With urinary symptoms	Without urinary symptoms	OR	95% CI	p value ^a	With urinary symptoms	Without urinary symptoms	OR	95% CI	p value ^a
Neurological	71%	46%	1.5	1.1–2.1	0.01	37%	28%	1.4	0.8–2.4	0.30
Rheumatological	54%	47%	1.4	0.8–1.6	0.51	29%	25%	1.4	0.6–2.2	0.69
Oral	83%	66%	1.3	1.01–1.6	0.05	43%	45%	0.9	0.6–1.5	0.83
Ocular	58%	51%	1.1	0.8–1.6	0.46	57%	56%	1.02	0.7–1.4	0.92
Respiratory	30%	26%	1.2	0.6–2.2	0.62	31%	24%	1.3	0.7–2.5	0.39
Sexual	58%	49%	1.2	0.8–1.7	0.34	34%	32%	1.08	0.6–1.9	0.78

^aChi-square test.

ing the EDSS to grade the findings. Twenty-five (21.7%) HTLV-I-infected subjects and 20 (17.4%) negative controls had EDSS scores greater than 0 but less than 2 ($p = 0.4$). Among the HTLV-I-infected subjects with $0 < EDSS < 2$, minimal abnormalities (score = 1) were found in the pyramidal ($n = 11$), urinary ($n = 8$), and intestinal ($n = 7$) functions. These findings did not differ from the findings found among seronegative controls (data not shown). When looking specifically at the frequency of hyperreflexia, 13 (11.3%) of HTLV-I-infected subjects and 7 (6.1%) of HTLV-I-negative subjects had increased deep tendon reflexes at least at one of the sites tested, but this difference was not statistically significant ($p = 0.16$). Among subjects who underwent physical examination of their joints, there was a higher percentage of HTLV-I-infected subjects with inflammatory signs compared to seronegative controls [presence of edema and/or warmth in 12 (23.5%) and decreased range of motion in 7 (14%) of the HTLV-I-infected subjects versus 0 and 1 (3.4%) of the seronegative controls, respectively].

DISCUSSION

In contrast to HIV-1, HTLV-I is thought to cause disease in only a minority of infected individuals. Most HTLV-I-infected persons are considered to be asymptomatic carriers. In this cross-sectional study, we found an association of HTLV-I infection with several symptoms and with findings on dental examination. HTLV-I-infected subjects, without a diagnosis of HAM/TSP, were more likely to report subjective neurological symptoms such as paresthesia and weakness, arthralgia, and erectile dysfunction. HTLV-I infection was also associated with the presence of gingivitis, periodontitis, and dry oral mucosa on dental examination. Urological symptoms were common among HTLV-I-infected subjects and those who reported urological symptoms were more likely to report neurological symptoms and to present oral abnormalities than HTLV-I-positive subjects without urological complaints.

Studies in the past have attempted to determine the health effects of HTLV-I infection but showed conflicting results. A

TABLE 4. PHYSICAL FINDINGS IN HTLV-I-INFECTED SUBJECTS AND MATCHED CONTROLS

	Case	Control	Matched OR ^a	95% CI	p	Adjusted OR ^{a,b}	95% CI	p
Neurological	($n = 115$)	($n = 115$)						
0 < EDSS < 2	25 (21.7%)	20 (17.4%)	1.3	0.7–2.6	0.4	1.2	0.5–2.5	0.7
Weakness	0	1 (0.86%)	—	—	—	—	—	—
Hyperreflexia	13 (11.3%)	7 (6%)	2.0	0.8–5.3	0.16	1.6	0.5–4.8	0.41
Rheumatological	($n = 86$)	($n = 115$)						
Edema/warmth	12 (23.5%)	0	—	—	—	—	—	—
Decreased range on motion	7 (14%)	1 (3.4%)	7.0	0.9–56.9	0.06	5.5	0.7–45.7	0.11
Dental	($n = 87$)	($n = 115$)						
Gingivitis	45 (51.7%)	26 (22.6%)	3.8	1.8–7.9	0.001	3.5	1.5–8.1	0.003
Periodontitis	23 (26.4%)	6 (5.2%)	10.00	2.3–42.8	0.002	7.70	1.7–35	0.008
Dry mucosa	15 (17.2%)	2 (1.7%)	7.50	1.7–32.8	0.007	7.50	1.5–38.4	0.016

^aConditional logistic regression.

^bAfter adjustment for income level.

cohort study in Jamaica comparing HTLV-I seropositive food handlers to seronegative controls failed to show a difference in the prevalence of current complaints such as trouble walking and painful or swollen joints, but showed lower body weight and lower body mass index among seropositive women and a trend toward higher prevalence of severe anemia in both HTLV-I-infected men and women.²² Two studies from the United States, in which a cohort of HTLV-I- and HTLV-II-infected and HTLV-I- and HTLV-II-uninfected blood donors was followed, found increased incidences of medically diagnosed bladder or kidney infection and arthritis among the HTLV-I-positive participants when compared to HTLV-I-negative controls.^{12,23}

Our finding of increased frequency of neurological symptoms, such as arm or leg weakness and hand or foot numbness, in HTLV-I-infected subjects is in accordance with other reports.^{12,24} HTLV-I-infected subjects, in the present study, also reported the most urological complaints at least as often as seronegative controls, although the differences were not statistically significant. Urinary frequency and nocturia were the symptoms most commonly reported in our study sample. It has been well established that urological complaints are prominent among patients with HAM/TSP.²⁵ HTLV-I-infected patients may develop these symptoms as early signs of neurological involvement. In a survey from Brazil, 10% of patients diagnosed with HAM/TSP reported urinary symptoms or impotence as their initial symptoms, prior to the development of gait disturbances.⁷ We also found a high prevalence of erectile dysfunction among HTLV-I carriers. Taken together, these findings demonstrate that HTLV-I carriers may present neurological abnormalities that can have an impact on their quality of life prior to being diagnosed with HAM/TSP. It is not known whether patients who already present with these symptoms are more likely to progress to HAM/TSP.

High proviral load and secretion of high levels of proinflammatory cytokines are associated with HAM/TSP.²⁶ It has been shown that a large proportion of HTLV-I carriers develop immunological responses, such as spontaneous lymphoproliferation and high production of interferon γ , similar to HAM/TSP patients.²⁷ HTLV-I carriers may develop other inflammatory diseases as a result of these immunological derangements. In our study, HTLV-I-positive subjects reported arthralgia lasting for more than 1 week and had evidence of synovitis more frequently than controls. These findings are in agreement with prior observations showing a possible association of HTLV-I infection with arthropathy in the absence of HAM/TSP.^{12,23,28} In this study, HTLV-I-infected subjects presented high rates of gingivitis, periodontitis, and dry oral mucosa. These oral findings could be explained by an exacerbated Th1 type immune response due to HTLV-I infection or, alternatively, by a direct influence of the virus. Of note, these oral findings remained statistically significant even after adjustment for income level. These findings may have been confounded by current or past smoking, for which we were unable to adjust.

We also observed that HTLV-I-infected subjects who reported urological symptoms were more likely to also report neurological symptoms and to have dental abnormalities than subjects who did not have urological complaints. This clustering of symptoms was not found among controls. Studies are in progress to determine if patients with urological and other find-

ings have immunological abnormalities or elevated HTLV-I proviral loads similar to HAM/TSP patients, which could predispose them to development of myelopathy and other inflammatory diseases.

Our study has some limitations worthy of mention. Since HTLV-I-infected subjects were aware of their serostatus, they could have been more likely to report symptoms that they assumed were related to HTLV-I infection. Also, we selected HTLV-I-infected subjects undergoing continued medical care at the HTLV-I multidisciplinary clinic, which could have created a selection bias. HTLV-I-infected subjects were slightly older, despite matching, and had lower income and educational levels than their seronegative controls, which may have influenced their reporting of symptoms and ability to access routine dental care. To reduce the likelihood of confounding, we adjusted our analyses for income level. Most of the associations observed persisted after multivariate analysis. Lastly, due to logistical constraints, different examiners evaluated HTLV-I-infected subjects and HTLV-I-negative subjects. To minimize the impact on our results, the physical examinations were standardized among study clinicians prior to enrollment of subjects and both examiners evaluated a subset of HTLV-I-infected patients, which yielded similar findings.

In summary, we found that HTLV-I infection is associated with a variety of clinical manifestations, which occur relatively often in patients who do not have or have yet to develop myelopathy. Our findings underscore the need for continued medical care of HTLV-I-infected individuals in order to promptly diagnose and potentially treat complications associated with HTLV-I infection. Further studies are needed to determine if HTLV-I-infected patients with clinical abnormalities are more likely to progress to HAM/TSP.

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