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Clinical Manifestations in Individuals with Recent Diagnosis of HTLV Type I Infection

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Abstract

Background—Human T-lymphotropic virus type 1 (HTLV-1) is known to cause HTLV-associated myelopathy (HAM)/tropical spastic paraparesis and adult T cell leukemia. A growing body of evidence links HTLV-1 infection with an increasing spectrum of disease, including uveitis, periodontal disease, arthropathy, sicca syndrome, and neurologic deficits.

Objectives—Despite recent findings, the natural history of HTLV-1 infection remains poorly defined. This study was designed to better characterize initial clinical and neurological findings in individuals diagnosed with HTLV-1 infection.

Study Design—We conducted a cross-sectional study of 71 individuals recently diagnosed with HTLV-1 and 71 uninfected age- and sex-matched blood donors in Salvador, Brazil. Subjects were administered a standardized questionnaire and underwent physical exam.

Results—HTLV-1 infected subjects were significantly more likely than controls to report complaints of hand and foot numbness (OR=5.3; 95% CI: 1.8-15.3; p=0.002 and OR=4.0; 95% CI: 1.3-12; p=0.013 respectively), difficulty running (OR=4.0; 95% CI: 1.1-14.2, p=0.032), nocturia (OR=5.0, 95% CI: 1.1-22.8, p=0.038), arthralgia (OR 3.3, 95% CI: 1.4-7.7, p=0.006), and photophobia (OR 3.3, 95% CI: 1.4-7.7, p=0.006).

Conclusions—Neurologic, ocular and rheumatologic complaints may be the first manifestations of HTLV-1 infection. Therefore, all patients presenting with initial diagnosis should be rigorously screened for these symptoms.

Keywords

HTLV-1; neurologic manifestations; clinical manifestations; neuropathy; natural history

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Background

It is estimated that 15-20 million people are currently infected with Human T-cell lymphotropic virus type 1 (HTLV-1) worldwide1, clustered in Africa, Central and South America, and Japan.2 Because its best-known complications, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T cell leukemia/lymphoma (ATLL), occur in less than 5% of infected individuals, HTLV-1 infection has been associated traditionally with low morbidity.3-7 However recent research has revealed biologic and epidemiologic evidence of association with a wider disease spectrum8, including uveitis,9-11 polymyositis,12, 13 arthropathy,14, 15 and sicca syndrome.16 In addition, multiple neurologic abnormalities, including erectile dysfunction,17 overactive bladder,18 weakness, hyperreflexia19 and peripheral neuropathy21-23 occur in HTLV-1 infected individuals without overt myelopathy, increasing the lifetime risk of HTLV-1-associated disease to greater than 30%.8

We previously reported a cross-sectional study demonstrating that HTLV-1 infected carriers were more likely than seronegative controls to report arm or leg weakness, hand or foot numbness, arthralgias, nocturia, and erectile dysfunction and to have gingivitis, periodontitis, and dry oral mucosa.23 However, this study was limited by the fact that HTLV-1 infected subjects were, on average, older than controls and were recruited from a HTLV-1 clinic where many had been followed **long term**, creating a potential selection bias.

Objectives

To better determine the prevalence of HTLV-1-associated disease and characterize early clinical and neurological findings, we conducted a cross-sectional study of individuals recently diagnosed with HTLV-1 and uninfected blood donors in Salvador, Brazil.

Study Design

Study site and population

This study was performed in Salvador, the capital city of Bahia State, in Northeastern Brazil, reported to have a seroprevalence of HTLV-1 infection of 1.76%.24, 25

Study Design and participants

Cases were patients referred to the HTLV-1 Clinic at the Hospital Universitario Prof. Edgard Santos from blood banks in Salvador, prenatal clinics, or through recent diagnosis of a family member. All new cases referred from January 2006 through July 2008, with serologic diagnosis by ELISA (Cambridge Biotech Corp., Worcester, MA) within the previous six months, were evaluated for inclusion. Inclusion criteria included confirmation of HTLV-1 diagnosis by Western Blot analysis (HTLV blot 2.4, Genelab, Singapore) and age between 18 and 60 years. Exclusion criteria included diagnosis of HAM/TSP,26 Hepatitis C or HIV infection, positive VDRL, and diabetes mellitus.

Seronegative controls were recruited from one of three major blood banks in Salvador (STS) at the time of blood donation, and matched 1:1 to cases by age (+/- 5 years) and sex. The study was approved by the Institutional Review Boards of the Hospital Universitario Prof. Edgard Santos and Weill Cornell Medical College. Informed consent was obtained from all subjects enrolled in the study.

Evaluations

A standardized questionnaire[23] was administered to all cases on first presentation to the HTLV-1 Clinic. Controls were administered the same questionnaire at the time of blood donation. All subjects underwent dental, rheumatological, and neurological examinations by a trained internist (S.P.). Exams were not blinded to HTLV-1 status because the subjects were aware of their infection status. Most patients with new diagnosis had no previous knowledge of the virus, and counseling was provided during interviews.

Statistical analysis

All analyses were performed using Stata 9.1 software (Stata Corporation, College Station, TX). Continuous variables were analyzed with an independent samples t-test. Matched univariate odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by conditional logistic regression for all variables with binary outcomes. Multiple conditional logistic regression was used to adjust for potential confounders. A p value of <0.05 was considered significant for statistical tests. No adjustment was made for multiple comparisons.

Results

Of 85 patients referred to the HTLV-1 clinic with new HTLV-1 diagnosis between January 2006 and July 2008, 72 cases met inclusion and exclusion criteria and were included in the study. Of these, 7 patients were referred from a prenatal clinic and one through diagnosis of a related blood donor. Demographic characteristics for these individuals were not statistically different than those of blood donors, and they were included in analysis. The remaining 64 patients were referred by blood banks. Given a limitation in the number of age-matched controls, 18 controls recruited by another study-trained internist (M.F.C) between 2004 and 2005 at the same blood bank were included in the study; only questionnaire data for these patients was used in the analysis. No control was available for one remaining case, thus leaving 71 cases of HTLV-1 infected blood donors, and 71 uninfected controls.

Table 1 summarizes the baseline characteristics of the study population. Case and control subjects were comparable with respect to age and ethnicity. HTLV-1 seronegative controls had a significantly higher socioeconomic status, determined by education and income. Each of these variables was analyzed as a potential confounder. Although education showed the strongest independent association with HTLV status (p=0.01), this variable was unavailable for a large proportion of controls. Consequently, all analyses were adjusted for income level (p=0.04), known for almost all participants.

As summarized in Table 2, HTLV-1 infected subjects were significantly more likely than controls to report complaints of hand and foot numbness [OR=5.3; 95% CI: 1.8-15.3; p=0.002 and OR=4.0; 95% CI: 1.3-12; p=0.013 respectively], difficulty running (OR=4.0; 95% CI: 1.1-14.2, p=0.032), nocturia (OR=5.0, 95% CI: 1.1-22.8, p=0.038), arthralgia (OR 3.3, 95% CI: 1.4-7.7, p=0.006), and photophobia (OR 3.3, 95% CI: 1.4-7.7, p=0.006). A higher percentage of subjects among cases than controls complained of arm and leg weakness (14.1% and 12.7% v. 1.4% respectively) and of difficulty with ambulation (11.3% v. 0%). A trend toward association between HTLV-1 infection and incontinence was also noted (OR=3.3; 95% CI: 0.92-12.1; p=0.067). In multivariate analysis, when data were adjusted for income, HTLV-1 infected subjects remained more likely to report nocturia (OR^a =4.0; 95% CI 0.88-19.1) but this difference was no longer statistically significant (p=0.073). All other associations remained statistically significant.

Table 3 summarizes findings on physical examination. Despite the higher prevalence of several subjective findings among HTLV-1 infected cases, objective physical exam failed to show any statistically significant differences between cases and seronegative controls. However, several important trends were noted. Two cases of weakness (3%) were noted among HTLV-1 infected subjects; no such cases were found among controls. A trend toward hyperreflexia was also observed among HTLV-1 infected patients (OR 2.8; 95% CI: 0.88-8.6; p=0.083). Decreased range of motion on rheumatologic exam was more common among seropositive subjects (7.4% v 0%), though this was not accompanied by signs of inflammation such as edema or warmth. Of note, no significant difference was noted between HTLV-1 infected and uninfected subjects in prevalence of periodontitis or dry mucosa.

Discussion

Over the last ten years, evidence has accumulated that, in addition to HAM/TSP and ATLL, HTLV-1 infection is capable of causing a variety of diseases including uveitis,[9-11] periodontal disease,[23, 27] sicca syndrome,[16] HTLV-1 associated arthropathy,[14, 15] and a large number of neurologic deficits.[17-22] It is particularly striking that these findings occur in a large group of individuals traditionally considered to be asymptomatic HTLV-1 carriers, indicating that morbidity associated with HTLV-1 is much higher than has been previously considered.[19, 28-31] Despite these contributions very little is known about the natural history of HTLV-1 infection. Specifically there is a gap related to information regarding the time between infection and appearance of objective clinical manifestations. In the present study we demonstrate that, in individuals with recently diagnosed HTLV-1 infection, subjective hand and feet numbness, arm and leg weakness, difficulty with ambulation and running, arthralgia, and photophobia were more frequent than in seronegative controls. However, given the unknown duration of infection prior to detection, we cannot determine conclusively that these are true early manifestations of infection.

The pathogenesis of diseases associated with HTLV-1 has been correlated with an elevated proviral load and an exaggerated type 1 immune response leading to inflammatory changes and adjacent tissue damage.[32, 33] These mechanisms have been documented not only in HAM/TSP, but also in other diseases associated with HTLV-1 infection, including infective dermatitis,[34] periodontal disease,[27] HTLV-1-associated arthropathy,[35] sicca syndrome,[16] and isolated neurologic deficits.[36] These findings clearly implicate HTLV-1 infection as central to the observed clinical pathology. Particularly pertinent to our findings is the fact that elevated levels of inflammatory cytokines such as INF-gamma, TNF-alpha, and chemokines have also been observed in up to 40% of asymptomatic carriers.[37-39] Further research is required to determine whether these serologic markers are risk factors for the development of future subjective or objective findings.

Compared with our previous cross-sectional study analyzing HTLV-1 carriers followed **long term** in a HTLV-1 clinic and seronegative controls,[23] we observed that, while neurologic complaints and arthralgia remained significantly more frequent in individuals with recent HTLV-1 diagnosis, increased prevalence of other manifestations such as overactive bladder, erectile dysfunction, and xerostomia did not reach statistical significance. It is possible that the reduced number of cases included in this study resulted in insufficient power to detect less marked differences. Alternatively, there may have been differences in self-report of symptoms related to differences in educational status between cases and controls. It is also possible that the manifestations detected in this study are, in fact, the early manifestations of HTLV-1 infection in this population, while periodontal disease, salivary gland involvement, and symptoms of overactive bladder and erectile dysfunction may occur later in the

infection. The absence of data on the duration of infection, however, precludes us from concluding this definitively.

The primary challenge in characterizing the natural history of HTLV-1 infection is that the time of infection cannot be determined in the large majority of infected individuals. As the majority of participants in this study were blood bank donors, the likelihood of transmission by injection drug use or transfusion is diminished; indeed, epidemiologic studies confirm low prevalences of both risk factors in our population.[40] Thus, it is probable that the majority were infected by either breast feeding or sexual transmission, both of which are associated with a slow, progressive course of disease.[8]

The symptoms described by HTLV-1 carriers in this study may be attributable to known HTLV-1 pathology. For example, the subjective symptoms of numbness and weakness are traditionally ascribed clinically to peripheral neuropathy, previously described in HTLV-1 carriers, though recently with some controversy. However, such symptoms are also observed in syndromes involving the central nervous system (CNS). In fact, MRI abnormalities observed in HAM/TSP are also detected in HTLV-1 carriers, suggesting that CNS, particularly spinal cord, involvement may contribute to these neurologic manifestations.[41, 42] Similarly, HTLV-1 infected patients with complaints of photophobia and arthralgia may be at higher risk of developing ocular or rheumatologic manifestations of HTLV-1 respectively.

Our data demonstrate the importance of studying individuals in the early phase of clinical disease in order to better clarify the natural history of HTLV-1 infection. **The** onset of the various manifestations associated with HTLV-1 likely occurs at different periods during the course of infection. Our findings suggest that weakness, sensory abnormalities, and ocular and rheumatologic complaints may be the first manifestations of HTLV-1 infection **to come to clinical attention**. Therefore, all patients presenting with initial diagnosis should be rigorously screened for these symptoms.

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Glossary

ATL	adult T-cell leukemia/lymphoma
CI	confidence interval
CNS	central nervous system
HAM/TSP	human T-lymphocytic virus-associated myelopathy/tropical spastic paraparesis
HTLV-1	human T-lymphotropic virus type 1
INF-gamma	interferon-gamma
TNF-alpha	tumor necrosis factor--alpha
OR	odds ratio

ORa adjusted odds ratio

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TABLE 1

DEMOGRAPHIC CHARACTERISTICS OF HTLV-1 INFECTED CASES AND UNINFECTED CONTROLS

	Case	Control	Matched OR[a]	95% CI	p
N	71	71			
Gender					
Male (%)	26 (36.6%)	26 (36.6%)			
Age, years, mean (SD)	40.2 (11.7)	40.3 (11.7)			0.96
Race (%)					
White	15 (21.7%)	14 (20%)	*referent*		
Mulatto	19 (27.5%)	24 (34.3%)	0.57	0.21-1.5	0.27
Black	34 (49.3%)	28 (40%)	0.95	0.41-2.2	0.91
Other	1 (1.5%)	4 (5.7%)	0.17	0.02-1.8	0.14
Education (%)					
≤8 years	26 (40%)	6 (12%)	*referent*		
>8 years	39 (60%)	44 (88%)	0.14	0.03-0.63	0.01
Income (%)					
≤4×MW[b]	61 (87.1%)	50 (71.4%)	*referent*		
>4×MW	9 (12.9%)	20 (28.6%)	0.42	0.18-0.96	0.04

[a] Conditional logistic regression

[b] Minimum wage is equivalent to US$291.50 per month

TABLE 2

UNIVARIATE AND MULTIVARIATE ANALYSES OF SYMPTOMS REPORTED BY HTLV-1 INFECTED CASES AND UNINFECTED CONTROLS

Symptoms	***Case***	***Control***	***OR[a]***	***95% CI***	***p***	***Adjusted 95% CI OR[b]***		***p***
Neurologic	n=71	n=71						
Hand numbness	25 (35.2%)	8 (11.3%)	5.3	1.8-15.3	0.002	7.0	2-23.6	0.002
Foot numbness	17 (23.9%)	5 (7%)	4.0	1.3-12	0.013	6.1	1.7-22	0.005
Arm weakness	10 (14.1%)	1 (1.4%)	-	-	-	-	-	-
Leg weakness	9 (12.7%)	1 (1.4%)	-	-	-	-	-	-
Difficulty Walking	8 (11.3%)	0 (0%)	-	-	-	-	-	-
Difficulty Running	12 (16.9%)	3 (4.2%)	4.0	1.1-14.2	0.032	4.0	1.1-14.8	0.038
Urologic	n=71	n=71						
Frequency	11 (15.5%)	20 (28.2%)	0.5	0.22-1.1	0.09	0.57	0.25-1.3	0.18
Nocturia	14 (19.7%)	6 (8.5%)	5.0	1.1-22.8	0.038	4.1	0.88-19.1	0.073
Urgency	12 (16.9%)	5 (7%)	2.8	0.88-8.6	0.083	3.0	0.81-11.1	0.101
Incontinence	10 (14.1%)	3 (4.2%)	3.3	0.92-12.1	0.067	3.0	0.8-11.3	0.105
Rheumatologic	n=71	n=71						
Arthralgia	25 (35.3%)	9 (12.7%)	3.3	1.4-7.7	0.006	3.5	1.4-8.5	0.005
Dental	n=71	n=71						
Xerostomia	16 (22.5%)	11 (15.5%)	1.5	0.67-3.3	0.321	1.6	0.7-3.6	0.27
Gingival bleeding	18 (25.4%)	11 (15.5%)	2.0	0.81-5	0.13	2.1	0.82-5.4	0.12
Ocular	n=71	n=71						
Dry eyes	14 (19.7%)	24 (33.8%)	0.52	0.25-1.1	0.082	0.59	0.28-1.2	0.17
Painful eyes	17 (23.9%)	14 (19.7%)	1.3	0.56-3.2	0.51	1.6	0.65-4	0.30
Photophobia	24 (33.8%)	8 (11.3%)	3.3	1.4-7.7	0.006	4.0	1.6-10.1	0.003
Sexual	n=25	n=24						
Erectile dysfunction	6 (24%)	2 (83%)	3.0	0.61-14.9	0.178	3.0	0.61-14.9	0.18

[a] Matched OR by conditional logistic regression

[b] Matched OR after adjustment for income

TABLE 3

UNIVARIATE AND MULTIVARIATE ANALYSES OF PHYSICAL FINDINGS IN HTLV-1 INFECTED CASES AND UNINFECTED CONTROLS

Findings	Case	Control	OR[a]	95% CI	p	Adjusted 95% CI OR[b]		p
Neurologic (%)	n=66	n=53						
Weakness	2 (3%)	0 (0%)	-	-	-	-	-	-
Hyperreflexia	14 (21.2%)	4 (7.5%)	2.8	0.88-8.6	0.083	2.8	0.88-8.7	0.082
Babinski	5 (7.6%)	2 (3.8%)	2.0	0.37-10.9	0.42	2.2	0.39-12.9	0.36
Rheumatologic	n=54	n=53						
Edema/warmth	1 (1.9%)	1 (1.5%)	1.0	0.06-16	1	1.0	0.06-16	1.0
Decreased ROM[c]	4 (7.4%)	0 (0%)	-	-	-	-	-	-
Dental	n=61	n=53						
Periodontitis	15 (24.6%)	15 (28.8%)	0.7	0.27-1.8	0.47	0.45	0.15-1.4	0.17
Dry mucosa	33 (54.1%)	27 (50.1%)	1.6	0.61-4.1	0.35	1.8	0.66-5	0.24

[a] Matched OR by conditional logistic regression

[b] Matched OR after adjustment for income

[c] Range of motion