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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.

1. Background

It is estimated that 15–20 million people are currently infected with human T-cell lymphotropic virus type 1 (HTLV-1) worldwide,[1] 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 spectrum,[8] 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, hyperreflexia[19] and peripheral neuropathy[21–23] 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

Abbreviations: 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; OR[a], 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.

many had been followed long term, creating a potential selection bias.

2. 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.

3. Study design

3.1. 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]

3.2. Study design and participants

Cases were patients referred to the HTLV-1 clinic at the Hospital Universitário 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 the 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 Universitário Prof. Edgard Santos and Weill Cornell Medical College. Informed consent was obtained from all subjects enrolled in the study.

3.3. 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.

3.4. 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.

4. 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 were 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;