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Soluble IL-2 Receptor and Beta-2 Microglobulin as Possible Serologic Markers of Neurologic Disease in HTLV-1 Infection

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Abstract

The human T-cell leukemia virus (HTLV-1) is the causative agent of a variety of neurologic diseases, including HTLV-1 Associated Myelopathy (HAM/TSP) and overactive bladder. Investigation of immune markers such as soluble interleukin-2 receptor (sIL-2R) and beta-2 microglobulin (B2M) has shown some promising results in distinguishing patients with neurologic disease from those with carrier status. The objective of the present study was to determine if plasma levels of sIL-2R and B2M are markers of neurologic disease in individuals infected with HTLV-1. The present study was divided into two parts. A cross-sectional study and a nested case control study. In the crosssectional study, HAM/TSP patients had higher plasma levels of B2M and sIL-2R than patients with overactive bladder and HTLV-1 carriers ($P < 0.01$ for all comparisons). For the nested case control study, the sIL-2 receptor test was able to distinguish patients with HAM/TSP from patients in the combined group of carriers and patients with overactive bladder with a sensitivity of 75.8% and false positive rate of 25.4%. Plasma levels of these markers did not change with the development of HAM/TSP and overactive bladder in HTLV-1 carrier patients. The present study has shown the importance of sIL-2 receptor in helping identifying HAM/TSP. However, the levels of these makers did not change significantly with the development of neurologic disease. © 2013 Wiley Periodicals, Inc.

Keywords

HTLV-1; HAM/TSP; neurologic disease; sIL-2R; beta-2 microglobulin

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INTRODUCTION

The human T-cell leukemia virus (HTLV-1) is a retrovirus that belongs to the *Retroviridae* family, the Orthoretrovirinae subfamily and to the deltaretrovirus genus [Gessain and Mahieux, 2012]. It is the causative agent of adult T-cell leukemia (ATL) [Yoshida et al., 1982] and a variety of neurologic diseases, including HTLV-1 Associated Myelopathy or Tropical Spastic Paraparesis (HAM/TSP) a progressive and debilitating disease [Gessain et al., 1985; Osame et al., 1986]. More recently, the virus has been linked to disturbances in the urogenital system of infected individuals [Poetker et al., 2011; Costa et al., 2012]. Overactive bladder has been recognized as an important manifestation of disease in patients previously considered carriers [Castro et al., 2007; Biswas et al., 2009; Sundberg et al., 2012].

The pathogenesis of HAM/TSP and other neurological manifestations of HTLV-1 infection is still poorly understood. Proviral load (PVL) has been identified as the single most important viral factor in the development of HAM/TSP, even though it is quite variable in different clinical forms of HTLV-1 [Jeffery et al., 1999; Kirk et al., 2011]. In addition, the levels vary in the same individual when multiple determinations are performed. From the point of view of the host immune system, some biomarkers have been investigated. Serum levels of soluble IL-2 receptor (sIL-2) and, more recently, beta-2 microglobulin (B2M) have shown some promising albeit limited, results [Birmann et al., 2009; Kirk et al., 2011].

B2M is a low molecular-weight protein that forms the common portion of the major histocompatibility complex (MHC) class I [Nakamuro et al., 1973; Hewitt, 2003]. The serum level of this molecule increases with decreased renal function in individuals with glomerular disease [Miyata et al., 1998]. In patients with intact renal function, B2M serum levels are a measure of immune stimulation. B2M has been shown to correlate with disease progression in individuals with AIDS [Fahey et al., 1990]. More recently, plasma proteome analysis has identified B2M to be elevated in the serum of patients with HAM/TSP [Kirk et al., 2011].

Activated T-cells release IL-2 and express the IL-2 receptor on their surface [Symons et al., 1988]. The IL-2 receptor is composed of three different subunits: alpha, beta, and gamma [Yang et al., 2011]. During T-cell activation, the alpha subunit is cleaved and released from the cell surface receptor as the sIL-2 receptor [Symons et al., 1988]. The sIL-2 receptor has been shown to be elevated in a variety of malignancies and inflammatory diseases such as rheumatoid arthritis [Symons et al., 1988]. High baseline serum sIL-2 receptor levels were associated with decreased survival in a study of HIV-infected patients prior to the advent of highly active antiretroviral treatment [Sipsas et al., 2003]. sIL-2 receptor and B2M are soluble immune activation markers and although not specific to HTLV-1, in the appropriate clinical setting their use may be of clinical utility for both diagnosis and prognosis of neurologic disease in patients with HTLV-1 infection.

The objective of the present study was to determine if plasma levels of sIL-2R and B2M are markers of neurologic disease in individuals infected with HTLV-1. Plasma levels of these

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markers were measured in individuals infected with the HTLV-1 virus who had HAM/TSP and overactive bladder and individuals who were carriers of the virus.

MATERIALS AND METHODS

Study Design

The study population consisted of subjects enrolled in the HTLV-1 multidisciplinary ambulatory of the University Hospital Professor Edgard Santos in Salvador, Bahia, Brazil. The study was divided into two stages. Stage one was a cross-sectional study of 119 subjects from the HTLV-1 ambulatory clinic who had stored plasma available. The plasma samples were randomly selected from three clinical groups: HTLV-1 carriers (n = 40), patients with HTLV-1 overactive bladder (n = 39), and HAM/TSP (n = 40). Selection was accomplished by random number generation using Microsoft Excel software. Individuals in the cohort who were 18–80 years old who had stored plasma in the laboratory of the Immunology service were included in the study. Overactive bladder was defined by the International Continence Society criteria and HAM/TSP diagnosis was based on the WHO criteria [Osame, 1990; Abrams et al., 2002]. The sample size was based on preliminary data on sIL-2 receptor suggesting that the mean difference between the HAM/TSP group and the carriers would be approximately 574 pg/ml with a standard deviation of 522. Assuming an alpha = 0.05, 18 subjects per group would provide 90% power to detect the expected effect size. Given that no preliminary data for B2M was available, it was assumed that levels would be similarly variable as in sIL-2 receptor. Thus, the same sample calculation was used for B2M levels.

The second stage of the study involved a nested case–control study, where the cases were patients who developed neurological disease (4 patients with HAM/TSP and 12 patients with overactive bladder) and had stored plasma both prior (at the time that their classification was HTLV-1 carriers) and after the diagnosis of neurologic disease. The controls (N = 14) were HTLV-1 carriers who had at least two samples of stored plasma. Patients were matched by gender, age ± 5 years, and time of follow-up from the time of the first evaluation to the time of neurologic disease diagnosis ± 2 years. To identify the patients described above, a member of the research team performed a comprehensive chart review. Cases were selected based upon clinician classification of disease staging. All patients signed an informed consent that authorized storage of plasma samples for immunologic studies. Patients with co-infection with the viruses HIV, HTLV-2, HCV, and HBV were excluded from the study. In addition, two patients from the control group in the case–control study were excluded because one of their plasma samples could not be located. The project was approved by the Institutional Review Boards of the University Hospital Professor Edgar Santos and Weill Cornell Medical College.

HTLV-1 Viral Markers

HTLV-1 PVL was determined using real-time PCR (Real-time TaqMan) in peripheral mononuclear blood cells (PBMCs) as previously described [Dehee et al., 2002].

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Immune Markers

Soluble interleukin-2 receptor (sIL-2R, R&D System, Minneapolis, MN) and B2M (Orgentec, Mainz, Germany) levels in plasma were determined by commercially available enzyme-linked immunosorbent assays (ELISA), performed according to manufacturer's instructions.

Statistical Analysis

Statistical analysis was performed using the Graphpad Prism software version 5.0. For the cross-sectional study, the continuous variables (B2M, sIL-2R) were compared across groups using the Kruskal–Wallis test followed by Dunn's multiple comparison test. For the nested case–control study, continuous variables were compared using the Wilcoxon rank-sum test. Categorical variables were compared by chi-square or Fisher's exact test as appropriate. A receiver operating characteristic (ROC) curve was generated using SPSS (IBM, version 20.0) software. For the ROC curve, data from subjects in the asymptomatic group and overactive bladder were combined for comparison against the HAM/TSP group. $P < 0.05$ was considered statistically significant.

RESULTS

Cross-Sectional STUDY

Age and income were similar among the three study groups. There was a lower proportion of women in the HTLV-1 carrier group when compared to the HAM/TSP and overactive bladder groups ($P = 0.04$), and the HAM/TSP group had a higher proportion of subjects who self-reported race as white (Table I).

Immune Markers

Plasma levels of sIL-2 R differed across the three study groups ($P < 0.0001$, Kruskal–Wallis test) and were higher in patients with HAM/TSP (median 1393.3 pg/ml, 1st quartile (Q1) 653.2 pg/ml, 3rd quartile (Q3) 2855.0 pg/ml, when compared to patients with overactive bladder (median 586.0, Q1 263.6 pg/ml, Q3 1279.0 pg/ml) and HTLV-1 carriers (median 473.4 pg/ml, Q1 152.6 pg/ml, Q3 867.1 pg/ml) with $P < 0.01$ and $P < 0.001$, respectively (Dunn's multiple comparison test) (Fig. 1A). Similarly, plasma levels of B2M were higher in HAM/TSP (median 3.990 μg/ml, Q1 3.585 μg/ml, Q3 4.900 μg/ml) than in both overactive bladder patients (median 3.310 μg/ml, Q1 2.480 μg/ml, Q3 3.720 μg/ml) and HTLV-1 carriers (median 3.000 μg/ml, Q1 2.493 μg/ml, Q3 4.300 μg/ml) $P < 0.01$ in both cases (Fig. 1B). There were no significant differences in the plasma levels of these immune markers between HTLV-1 carriers and patients with overactive bladder.

Neither the plasma levels of B-2 microglobulin nor the levels of sIL-2R correlated with the HTLV-1 PVL within each group ($P > 0.05$, data not shown).

ROC Curve

To test for the ability of sIL2-R, B2M, and PVL test to discriminate between patients with HAM/TSP from HTLV-1 carriers and overactive bladder patients (latter two groups combined), ROC curves were constructed (Fig. 2). The B-2 microglobulin ELISA test was

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able to discriminate patients with HAM/TSP with a 72% sensitivity and 35% false positive rate (area under the curve of 0.74, 95% CI 0.65–0.85), $P < 0.0001$) using a cut-off value of 3.65 μg/ml. sIL-2R significantly discriminated between the groups with a sensitivity of 75.8% and false positive rate of 25.4% (area under the curve of 0.80 (95% CI 0.71–0.89, $P < 0.0001$)) using a cut-off value of 922.5 pg/ml. PVL discriminated between HAM/TSP and the other two groups with a sensitivity of 73% and false positive rate of 40% (area under the curve of 0.72 (95% CI 0.62–0.83, $P < 0.0001$)) using a cut-off of 4.74 log, (Fig. 2). None of the three tests was sensitive enough to discriminate patients with overactive bladder from HTLV-1 carriers.

Nested Case–Control Study

Age, proportion of women, and duration of follow-up were equally distributed between the two groups as expected given the matching (Table II). To test if the plasma levels of the potential biomarkers changed with the development of neurologic disease, blood levels of sIL-2R and B2M were tested prior to and after the diagnosis of neurologic disease. Matched asymptomatic carriers had measurements of the biomarkers at two different points in time for comparison's sake. There were no significant changes in the levels of both sIL-2R (Fig. 3A) and B2M (Fig. 3B) for patients who developed neurologic disease (HAM/TSP and/or HTLV-1 overactive bladder) ($P = 0.50$ and 0.56, respectively). Similarly, there were no significant changes in the levels of sIL-2R (Fig. 3C) and B2M (Fig. 3D) between the first and second evaluation in HTLV-1 carriers ($P = 0.46$ and 0.09, respectively). At time T0, sIL-2 levels and B2M levels did not differ significantly between the carrier group and the neurological disease group.

DISCUSSION

Although the pathogenesis of neurologic disease in HTLV-1 infection is not fully understood, it is known that the host immune response plays an important role in the development of disease. Thus, it is important to characterize parameters that differ significantly between individuals that are carriers from those who develop neurologic disease. In HAM/TSP, a progressive and debilitating neurologic disease, markers of immune activation have been shown to be capable of distinguishing individuals with HAM/TSP from HTLV-1 carriers [Olindo et al., 2005; Kirk et al., 2011]. In this study, it was shown that patients with HAM/TSP produce higher levels of sIL-2 receptor when compared to patients with overactive bladder and HTLV-1 carriers. Furthermore, the establishment of disease markers is important given that often times clinical diagnosis of HAM/TSP can be problematic.

Although the WHO criteria for the diagnosis of HAM/TSP have been well accepted since the late 1980s, uncertainty in the diagnosis can still be found, particularly in cases where patients do not fulfill the complete WHO criteria [De Castro-Costa et al., 2006]. These difficulties are apparent in the recent attempts to establish a new classification for the disease, which recognize less severe forms of neurologic diseases as early manifestations of HAM/TSP [De Castro-Costa et al., 2006; Grassi et al., 2011]. The sensitivity of 75.8% found in the ELISA test for sIL-2 receptors in the present study is comparable to the 78.2%

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sensitivity of the PVL test in identifying true HAM/TSP patients [Furtado Mdos et al., 2012]. In the present study, the PVL test was less sensitive (73%) to identify patients with HAM/TSP and had an unacceptable false positive rate of 40%. Although there was a significant difference in the plasma levels of sIL-2 receptor in HAM/TSP and overactive bladder patients, the test was unable to distinguish these two clinical forms. The levels of PVL overlap significantly between individuals that are carriers and individuals with HAM/TSP [Jeffery et al., 1999; Kirk et al., 2011]. This same variability is found in the levels of sIL-2 receptors. Thus, these parameters remain complementary to the diagnosis of HAM/TSP, given the wide variability of the levels among individuals within the same clinical status.

Recently, B-2 microglobulin has been identified as a possible marker for disease status in patients with HAM/TSP [Kirk et al., 2011]. Using ELISA, a simpler and more readily available method to quantify this molecule, it was observed that HAM/TSP patients have significantly higher median levels when compared to patients with overactive bladder and HTLV-1 carriers. However, the sensitivity of 72% of the test was lower compared to the sensitivity of B2M when using a more sophisticated method (79%) [Kirk et al., 2011]. As with the sIL-2 receptor, the B-2 microglobulin test was unable to distinguish patients with overactive bladder from carriers or HAM/TSP.

Possible confounding variables included a higher percentage of women in the HAM/TSP group when compared to the HTLV-1 carrier group, although previous studies have found that gender distribution was not a significant factor in explaining the heterogeneity of sIL-2R levels [Liu et al., 2011]. In addition, there was a higher percentage of whites (self-designated) in the group with HAM/TSP in the crosssectional study, which might represent a non-identified source of bias during the patient selection process.

Since biomarkers are important to follow progression of disease, the levels of sIl-2R and B2M were measured in the plasma of patients that were HTLV-1 carries who had progressed to neurologic disease while being followed in the cohort. The median levels of the two markers did not differ significantly between the time prior to the development of neurologic disease and the time after the development of disease. The levels of both markers were also similar at time T0 for both groups. Thus, these two markers might prove important to help characterize clinical status. Although the present study failed to show the importance of sIL-2R and B2M to monitor neurologic disease progression in HTLV-1 infection, future studies where longitudinal data based upon the new classification of HAM/TSP [De Castro-Costa et al., 2006] are needed in order to determine if the levels of these markers change across the different stages of the disease.

In conclusion, the present study has shown the importance of sIL-2 receptor in helping identifying HAM/TSP. However, neither B2M levels nor sIL-2 receptors were helpful in distinguishing mild neurologic disease from carriers. In addition, the level of these markers did not appear to be significant in monitoring neurologic disease progression, but rather seem to be markers of late disease in patients with HAM/TSP. However, given the small sample size in the nested-case control study, prospective, larger studies are needed to

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determine if these markers are important for monitoring neurologic disease progression in HTLV-1 infection.

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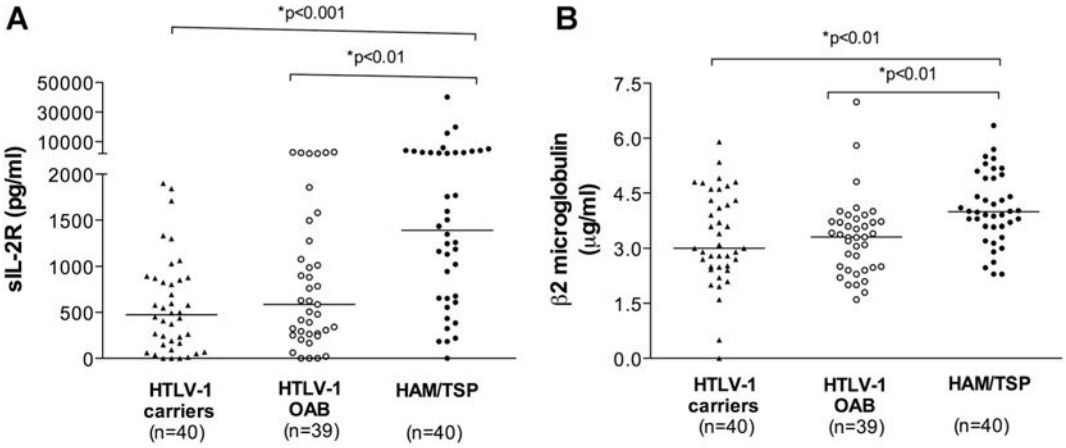

Fig. 1.

Plasma levels of sIL-2R and B2M. Median levels of (**A**) interleukin-2 soluble receptor (sIL-2R, pg/ml) and (**B**) B-2 microglobulin (mg/ml) observed in plasma of HTLV-1 carriers (filled triangle), HTLV-1 patients with overactive bladder (open circle) and HAM/TSP patients (filled circle). *Kruskal–Wallis test.

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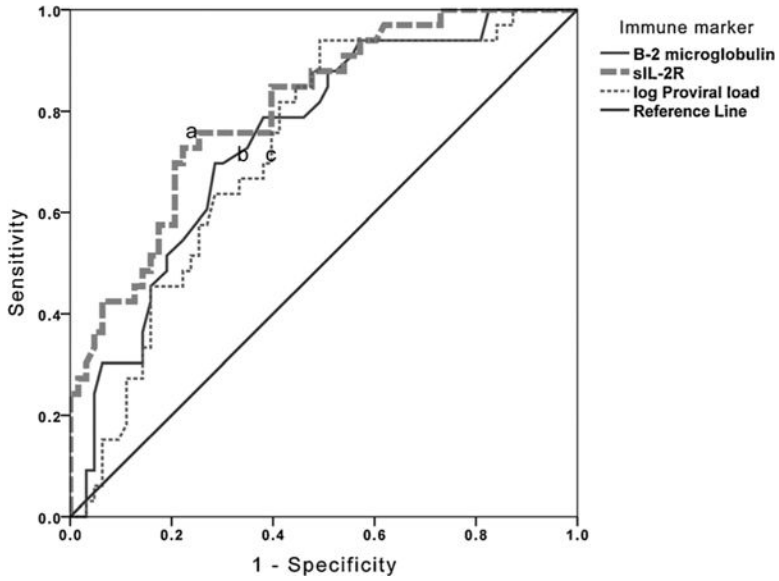

Fig. 2.

ROC curve of (a) sIL-2 receptor (thick, dotted line, area under the curve 0.80, 95% CI 0.71–0.89, $P < 0.0001$), (b) beta-2 microglobulin (solid line, area under the curve of 0.74, 95% CI 0.646–0.847, $P < 0.0001$), and (c) log proviral load (thin dotted line, area under the curve 0.72, CI 95% CI 0.62–0.83, $P < 0.0001$) in 40 patients with HAM/TSP compared to combined data of 40 HTLV-1 carriers and 39 HTLV-1 overactive bladder.

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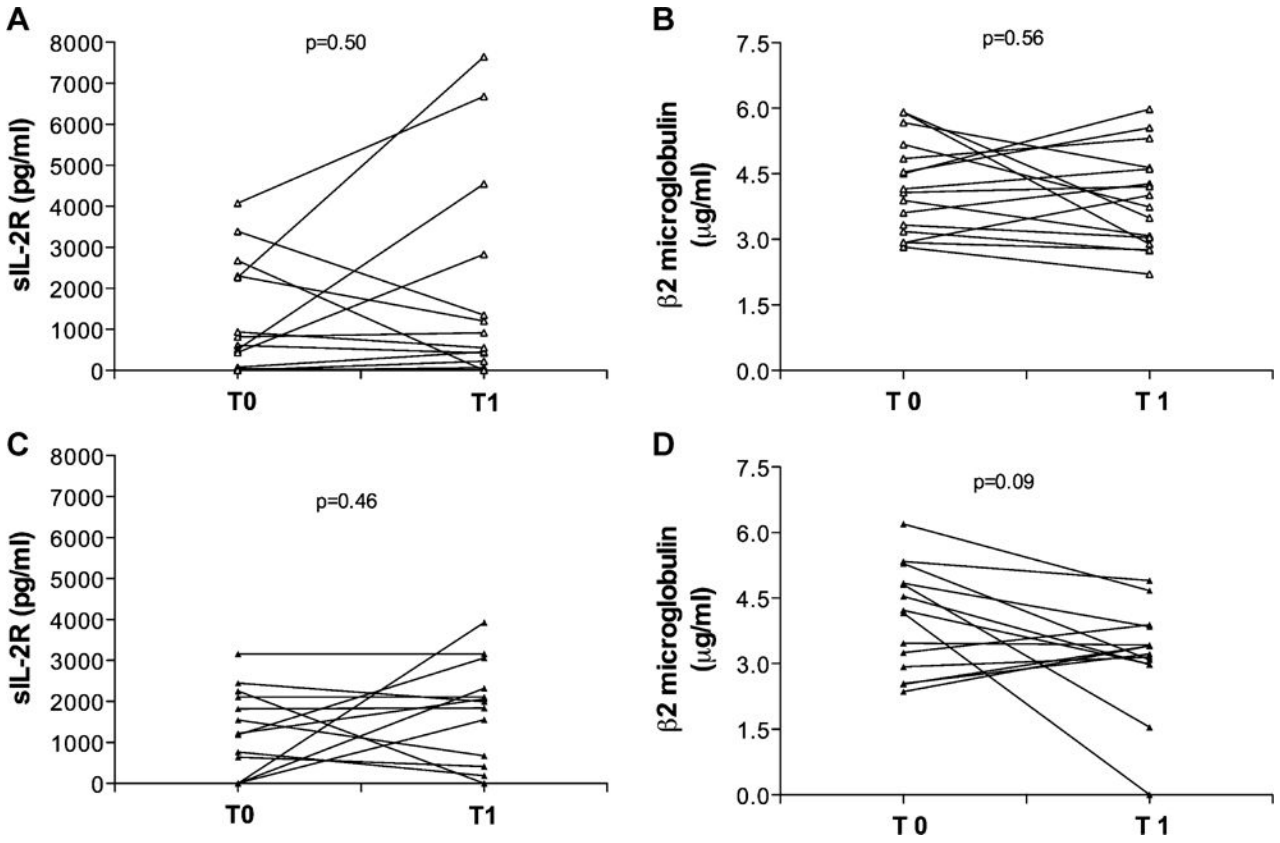

Fig. 3.

Plasma levels of sIL-2R and B2M at times T0 and T1. Plasma levels of Interleukin-2 soluble receptor (sIL-2R, pg/ml) in patients with neurologic disease (**A**) and HTLV-1 carriers (**C**) and B-2 microglobulin plasma (μg/ml) levels in neurologic disease (**B**) and carriers (**D**) at times T0 and T1. T0 is the time of the first evaluation for carriers and time of evaluation prior to the diagnosis of neurologic disease for patients with disease progression, and T1 is the time at second evaluation for carriers and evaluation after the diagnosis of neurologic disease for patients with disease progression. Statistical analysis with Wilcoxon rank-sum test.

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TABLE I

Demographic Characteristics of 119 Patients Infected With HTLV-1

	Asymptomatic (n = 40)	HTLV-1 OAB (n = 39)	HAM/TSP (n = 40)	*P*-value
Female, n (%)	15 (37.5%)	22 (56%)	26 (65%)	$P = 0.04^a$
Age, median (range)	49.5 (34–72)	49 (33–69)	52.5 (20–70)	$P = 0.89^b$
Race (self-reported) (n)				
Black	18	16	4	$P = 0.001^a$
White	4	4	17	
Mixed race	10	18	17	
Other	1	0	0	
Unknown	7	1	2	
Income (n)				
<01	5	6	4	$P = 0.67^a$
>01 to <04	28	27	27	
>04 to <10	6	5	5	
>10	1	0	3	
Proviral load	9,660.0 (0.0–1,234,806.0)	72,425.0 (0.0–504,140.0)	133,068.0 (34.7–415,054.0)	$P = 0.0001^b$

[a]Fisher exact chi-square test. A significant difference was found in the proportion of females between the groups of HTLV-1 carrier and HAM/TSP. The HAM/TSP group had higher proportion of whites and lower proportion of blacks when compared to the HTLV-1 carrier and the HTLV-1 OAB groups.

[b]Kruskal–Wallis test.

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TABLE II

Demographic Characteristics of Patients With Neurologic Disease (Cases) and HTLV-1 Carriers (Controls)

	Controls (HTLV-1 carriers) (n = 14)	**Cases (HTLV-1 neurologic disease) (n = 16)**	***P*-value**
Female, n (%)	9 (64.3%)	10 (62.5%)	$P = 0.91^a$
Age, median (range)	49.0 (29–63)	45 (20–64)	$P = 0.69^b$
Time of neurologic disease diagnoses/time of follow-up for carriers, median (range in years)	5.5 (1–7)	3.5 (1–8)	$P = 0.21^b$

[a]Fisher exact chi-square test.

[b]Mann–Whitney test.