Neurologic abnormalities in HTLV-I– and HTLV-II–infected individuals without overt myelopathy

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ABSTRACT

Background: Human T-lymphotropic virus (HTLV) type I is the causative agent of HTLV-associated myelopathy (HAM)/tropical spastic paraparesis, and a number of HAM cases with HTLV-II infection have also been reported. However, despite some reports, it is unclear whether HTLV-I or -II infection is associated with other neurologic manifestations.

Methods: An analysis of medical histories and screening neurologic examinations from a prospective cohort of 153 HTLV-I, 388 HTLV-II, and 810 HTLV-seronegative individuals followed up for means of 11.5, 12.0, and 12.2 years was performed. Participants diagnosed with HAM were excluded. We calculated odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for age, sex, race or ethnicity, income, educational attainment, body mass index, alcohol and cigarette consumption, injection drug use, diabetes, and hepatitis C virus status, using generalized estimating equations for repeated measures.

Results: HTLV-I and -II participants were more likely than seronegative participants to have leg weakness (ORs 1.67 [95% CI 1.28–2.18] and 1.44 [1.16–1.78]), impaired tandem gait (ORs 1.25 [95% CI 1.07–1.47] and 1.45 [1.27–1.64]), Babinski sign (ORs 1.54 [95% CI 1.13–2.08] and 1.51 [1.18–1.93]), impaired vibration sense (ORs 1.16 [95% CI 1.01–1.33] and 1.27 [1.14–1.42]), and urinary incontinence (ORs 1.45 [95% CI 1.23–1.72] and 1.70 [1.50–1.93]). For both HTLV-I and -II participants, higher odds of sensory neuropathy by monofilament examination were no longer significant after adjustment for confounding.

Conclusions: These results provide strong evidence that human T-lymphotropic virus (HTLV)-I and -II are associated with a spectrum of predominantly motor abnormalities in patients without overt HTLV-associated myelopathy. Further investigation of the clinical course and etiology of these abnormalities is warranted. ***Neurology*® 2009;73:781–789**

GLOSSARY

ATL = adult T-cell leukemia/lymphoma; **CI** = confidence interval; **HAM** = human T-lymphotropic virus–associated myelopathy; **HOST** = HTLV Outcomes Study; **HTLV** = human T-lymphotropic virus; **OR** = odds ratio; **ORa** = adjusted odds ratio.

Human T-lymphotropic virus (HTLV) types I and II are human retroviruses first described in the early 1980s.[1,2] HTLV-I is the causative agent of HTLV-associated myelopathy (HAM; also known as tropical spastic paraparesis), a progressive neurologic disorder characterized by leg weakness, diffuse hyperreflexia, clonus, loss of vibration sense, and detrusor insufficiency leading to bladder dysfunction. Of the millions of individuals infected with HTLV-I worldwide,[3] it is estimated that approximately 4% will develop HAM during their lifetimes.[4] Although the

Supplemental data at www.neurology.org

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role of HTLV-II in HAM is somewhat controversial, there is increasing evidence that supports an association, and a recent critical review has recognized the entity.[5]

Several studies suggest that HTLV may be associated with a wider spectrum of neurologic manifestations that do not meet diagnostic criteria for HAM. These symptoms and conditions may later progress to HAM or constitute isolated neurologic syndromes associated with HTLV infection. Sensory neuropathy,[6-8] gait abnormalities,[9,10] bladder dysfunction,[6,9-12] erectile dysfunction,[13,14] ALS,[15] mild cognitive deficits,[16] and rarely, motor neuropathies[6,8,13,17-19] have all been reported among HTLV-I–infected individuals without HAM. Although less research has focused on HTLV-II, sensory neuropathy has been observed with HTLV-II alone[20] and with HIV coinfection.[20-23] A spinocerebellar syndrome has also been documented in a few case reports of HTLV-I– and -II–infected patients.[24]

A better understanding of the neurologic abnormalities associated with HTLV infection is important for the clinical care of infected patients. The etiology and pathogenesis of these abnormalities are poorly defined, and it is unclear whether they are a precursor to the development of HAM or part of a broader spectrum of HTLV-associated neurologic morbidity. Previous findings on HTLV-associated neurologic abnormalities other than HAM are derived from case series and cross-sectional studies and have been mostly limited to the study of HTLV-I. As part of the HTLV Outcomes Study (HOST), we investigated the association of HTLV-I– and -II–infected individuals with neurologic abnormalities in a large cohort of HTLV-I– and -II–infected individuals followed prospectively with standardized neurologic screening examinations for more than 15 years.

METHODS

Study design and participants. This was a prospective, multicenter cohort study of individuals with HTLV-I or -II infection detected at the time of attempted blood donation at 5 major US blood centers (Baltimore/Washington, Detroit, Oklahoma City, San Francisco, and Los Angeles) and HTLV-seronegative donors enrolled at the same centers. Details of the cohort enrollment and follow-up procedures have been previously published.[25] Briefly, 155 HTLV-I, 387 HTLV-II, and 799 HTLV-seronegative persons were enrolled into the cohort in 1990 through 1992 and were followed up every 2 years. Five HTLV-I, 4 HTLV-II, and 11 HTLV-seronegative persons were additionally enrolled during the sixth visit in 2002 through 2003. HTLV-seronegative controls were matched 2:1 to HTLV-I– and -II–infected persons within each stratum based on age, sex, race or ethnicity, blood center, and type of blood donation (community, autologous, or directed). For this analysis of neurologic abnormalities, the inclusion criterion was completion of the interview at any visit. Subjects were excluded if they had a diagnosis of HAM or adult T-cell leukemia/lymphoma (ATL).

Laboratory testing for HTLV-I or -II seropositivity has been previously described. HTLV serologic status was determined by enzyme immunoassay, followed by confirmatory Western blot. A central laboratory performed HTLV-I vs -II typing with a type-specific serologic assay, PCR, or both. Serologic typing correlated with results from a type-specific PCR assay. All participants at baseline and at visit 5 were tested and found seronegative for HIV. Neither vitamin B_{12} nor syphilis serology was measured systematically, but subjects with overt neurologic findings suggestive of HAM underwent testing for these potential causes of neurologic disease, and most were negative.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the University of California San Francisco Committee on Human Research and by institutional review boards at other participating institutions, and all subjects gave written informed consent.

Neurologic history and examination. Each visit included a standardized questionnaire focused on symptoms of neurologic, urinary tract, and hematologic disease; a standardized screening examination; and phlebotomy for complete blood count and repository specimens. The neurologic portion of the screening examination was performed by trained study nurses and tested heel, toe, and tandem gait; biceps reflex, patellar reflex, and extensor plantar response (Babinski sign); and vibration sensation, as previously described[4] (see appendix e-1 on the *Neurology*® Web site at www.neurology.org). Leg muscle weakness was also screened for by instructing the subject to rise from a chair of standard height without using the hands. Nurses received training in the examination procedures at the beginning of each set of visits by a board-certified academic neurologist (J.E.) and were supervised by the study physician at each center.

Beginning at visit 5, a 5.07 (10-g) Semmes–Weinstein monofilament was used to test for sensory neuropathy at 3 sites on the distal lower extremity using procedures adapted from those recommended by a consensus conference on sensory neuropathy.[26,27] For the monofilament examination outcome variable, subjects were required to have decreased sensation at a minimum of 2 of the 6 lower extremity sites examined to be considered abnormal, to minimize false-positive readings. Body mass index was calculated from self-reported height and weight, and diabetes was determined by self-report. The examinations were not performed blinded to HTLV status because the subjects were aware of their infection status and counseling was providing during these examinations.

Statistical methods. Data through visit 7 conducted in 2004 through 2007 were available for analysis. Visit 4 in 1998 was excluded from the analysis because no examinations were performed during that visit. The Kaplan–Meier method was used to generate survival curves for the onset and recurrence of neurologic abnormalities, and the log-rank test was used to test for associations with HTLV status. Gait examination findings (impaired heel, toe, and tandem gait), reflex findings (biceps reflex, patellar reflex, and Babinski sign), and urinary tract symptoms (prevoid and postvoid urgency and incontinence) were each

Table 1 Baseline characteristics of the study population by HTLV serologic status*

Characteristic	HTLV-I (n = 153)	HTLV-II (n = 388)	HTLV-seronegative (n = 810)
Age			
Mean (range), y	46 (18–78)	41 (17–78)	44 (17–79)
17–35 y	31 (20.3)	102 (26.3)	208 (25.7)
36–45 y	50 (32.7)	183 (47.2)	292 (36.0)
46–55 y	37 (24.2)	72 (18.5)	179 (22.1)
56–65 y	25 (16.3)	21 (5.4)	94 (11.6)
>65 y	10 (6.5)	10 (2.6)	37 (4.6)
Sex			
Female	110 (71.9)	285 (73.4)	552 (68.2)
Male	43 (28.1)	103 (26.6)	258 (31.8)
Race or ethnicity			
Black	62 (40.8)	126 (32.7)	248 (30.6)
White	58 (38.2)	136 (35.3)	310 (38.3)
Asian, Hispanic, or other	32 (21.0)	123 (32.0)	252 (31.1)
Education			
High school or less	55 (36.2)	155 (40.0)	148 (18.3)
Some college	62 (40.8)	180 (46.4)	365 (45.0)
College graduate or more	35 (23.0)	53 (13.6)	297 (36.7)
Income			
<$30,000	58 (38.9)	170 (44.3)	203 (25.2)
$30,000–<$50,000	48 (32.2)	121 (31.5)	247 (30.8)
≥$50,000	43 (28.9)	93 (24.2)	353 (44.0)
Center			
Baltimore/Washington	35 (22.9)	51 (13.2)	126 (15.6)
Detroit	33 (21.6)	40 (10.3)	104 (12.8)
Los Angeles	43 (28.1)	206 (53.1)	349 (43.1)
San Francisco	27 (17.6)	68 (17.5)	157 (19.4)
Oklahoma City	15 (9.8)	23 (5.9)	74 (9.1)
Blood donor type			
Autologous	26 (17.9)	39 (10.2)	111 (13.9)
Allogeneic	119 (82.1)	345 (89.8)	688 (86.1)
Body mass index			
Underweight or healthy weight: <25 kg/m^2	43 (28.6)	100 (25.8)	185 (23.1)
Overweight: 25–29.9 kg/m^2	52 (34.7)	144 (37.2)	337 (42.1)
Obese: >30 kg/m^2	55 (36.7)	143 (37.0)	278 (34.8)
Smoking history			
Nonsmoker	60 (39.2)	95 (24.5)	353 (43.6)
1–15 packs/y	30 (19.6)	122 (31.4)	178 (22.0)
>15 packs/y	38 (24.9)	85 (21.9)	175 (21.6)
Missing	25 (16.3)	86 (22.2)	104 (12.8)
Alcohol intake			
Nondrinker	15 (9.8)	13 (3.3)	53 (6.6)
1–14 drinks/wk	105 (68.6)	248 (63.9)	611 (75.4)
>14 drinks/wk	8 (5.2)	41 (10.6)	43 (5.3)
Missing	25 (16.4)	86 (22.2)	103 (12.7)

—Continued

combined to derive survival curves. Leg weakness and impaired vibration sense were also assessed using survival curves. Subjects were censored at the visit number during which the abnormality was detected or at the last follow-up visit for subjects without an abnormality. Time-to-event analyses were conducted using STATA 10 software (StataCorp LP, College Station, TX).

To account for repeated examination of the same subjects, odds ratios (ORs) and 95% confidence intervals (CIs) for HTLV-I and -II associations with neurologic signs and symptoms compared with seronegative subjects were calculated using generalized estimating equations for repeated measures. We first calculated unadjusted ORs using reduced models that included only HTLV status, visit number, and blood center as independent variables. We then generated adjusted ORs for HTLV-I and -II associations with neurologic outcomes using multivariate models that included HTLV status, visit number, blood center, age at baseline, sex, race, educational attainment, cigarette and alcohol consumption, injection drug use, body mass index, diabetes, and hepatitis C virus status as independent variables. We also assessed HTLV-I and -II associations with work-loss days using adjusted multivariate models. Repeated-measures analyses were conducted using SAS 9.1 software (SAS Institute, Cary, NC).

We compared the proportions of HTLV-infected and HTLV-seronegative participants with impaired sensation by monofilament examination using χ^2 and Fisher exact tests. We also compared their mean number of work-loss days for each visit using the Student t test. The χ^2 test, Fisher exact test, and Student t test were performed as 2-sided tests using STATA 10 software.

RESULTS **Study population and follow-up.** After excluding 9 participants with HAM and 1 patient with ATL, we included 153 HTLV-I, 388 HTLV-II, and 810 HTLV-seronegative participants in this analysis. The baseline characteristics of the study population are provided in table 1. The HTLV groups and seronegative participants were comparable with respect to age, sex, race or ethnicity, blood center, type of blood donation (allogeneic vs autologous), and body mass index except for slightly higher proportions of African-Americans among HTLV-I participants. HTLV-seronegative participants had the highest socioeconomic status, as indicated by educational attainment and income. Pack-years of cigarette smoking and amount of alcohol intake were higher in HTLV-II participants, and they also more frequently reported a lifetime history of injection drug use or current injection drug use. However, most injection drug use was remote, with current injection drug use reported by only 2% of HTLV-II participants and none of the HTLV-I or HTLV-seronegative participants. Hepatitis C seropositivity was substantially higher among HTLV-II participants.

The mean follow-up time was 12.0 years for all 1,351 participants, including late enrollees, and was 11.5 years for the HTLV-I group, 12.0 years for the HTLV-II group, and 12.2 years for the HTLV-seronegative group.

Clinical findings. Disease-free survival curves for 5 types of neurologic abnormalities by HTLV status

Table 1 Continued

Characteristic	HTLV-I (n = 153)	HTLV-II (n = 388)	HTLV-seronegative (n = 810)
Hepatitis C status†			
Negative	123 (80.4)	266 (68.6)	788 (97.3)
Positive	6 (3.9)	66 (17.0)	9 (1.1)
Missing	24 (15.7)	56 (14.4)	13 (1.6)
Injection drug use			
Never	150 (98.7)	295 (76.2)	799 (98.8)
Past	2 (1.3)	84 (21.7)	10 (1.2)
Current	0 (0)	8 (2.1)	0 (0)

Data are presented as number (percentage).
*148 HTLV-I, 384 HTLV-II, and 799 HTLV-seronegative participants were enrolled in 1990–1992; all other participants were enrolled in 2002–2003. Unless otherwise indicated, missing data were <5%.
†Hepatitis C status was measured in 2000–2001.
HTLV = human T-lymphotropic virus.

are presented in figure 1. Compared with HTLV-seronegative subjects, HTLV-I– and HTLV-II–infected subjects experienced lower survival to leg weakness, impaired gait, hyperreflexia, impaired vibration sense, and urinary tract abnormality (log-rank $p < 0.01$ for all abnormality types). There were no significant differences between HTLV groups in survival to any abnormality, nor did recurrence differ by HTLV status (data not shown).

In unadjusted comparisons with seronegative participants, HTLV-I and -II infections were both associated with leg weakness, impaired heel walking, impaired toe walking, impaired tandem gait, Babinski sign, and impaired vibration sense (table 2). All of these associations persisted after adjustment for confounding, except for that between HTLV-I infection and impaired toe walking. Although the proportions of participants with impaired sensation by monofilament examination differed by HTLV status for visits 5 and 6 using the χ^2 test (table 3), adjusted ORs from the repeated-measures analysis were not significant (table 2). Self-reported urinary tract symptoms indicated higher rates of prevoid and postvoid urgency and incontinence in HTLV-I and -II participants in both the unadjusted and adjusted analyses (table 2).

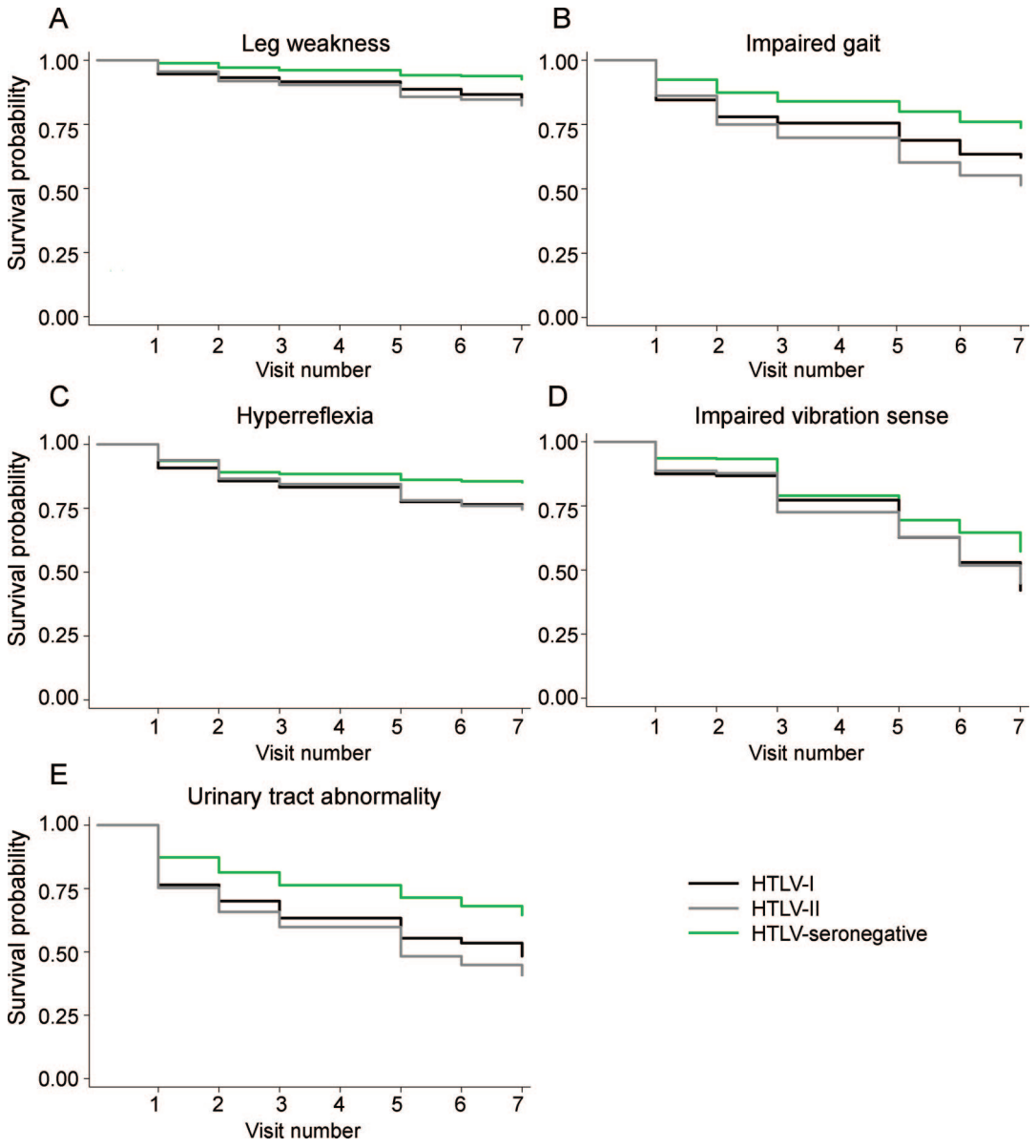
The overall mean number of work-loss days was 5.5 for HTLV-I, 14.5 for HTLV-II, and 6.1 for HTLV-seronegative subjects. At each of the 6 visits with complete data (visit 4 was not included), the mean number of work-loss days was greater for HTLV-II participants when compared with that for HTLV-I and HTLV-seronegative participants ($p < 0.0001$ at all visits; figure 2). Using multivariate repeated-measures analysis to control for confounding, HTLV-II participants were shown to report 14.8 (95% CI 4.9–44.6, $p < 0.0001$) more work-loss days on average as compared with HTLV-seronegative participants. There was no significant difference in mean number of work-loss days between HTLV-I and HTLV-seronegative participants (OR 0.88, 95% CI 0.11–7.0, $p = 0.9015$).

As previously reported, a cumulative 4% of HTLV-I–infected participants and 1% of HTLV-II–infected participants have developed HAM over the course of the HOST study, which is now in its 16th year.[4] Although they were excluded from the current analysis, we examined the records of all incident cases of HTLV-I HAM (n = 2) and HTLV-II HAM (n = 2) for neurologic abnormalities before their diagnosis of overt HAM. All 4 participants experienced at least some signs of leg weakness, impaired gait, impaired vibration sense, or urinary tract abnormality at visits before diagnosis.

DISCUSSION In this large prospective cohort study, HTLV-I– and -II–infected participants had increased odds of motor and sensory neurologic signs and bladder symptoms compared with HTLV-seronegative participants. In general, both HTLV-I– and -II–infected participants were more likely than HTLV-seronegative participants to report bladder dysfunction and manifest examination abnormalities, including leg weakness, impaired gait, hyperreflexia, and impaired vibration sense. Neither group had a higher frequency of sensory peripheral neuropathy compared with HTLV-seronegative participants after adjusting for potential confounding variables. These results support some, but not all, previous studies that demonstrated the association of HTLV with a spectrum of neurologic abnormalities other than HAM.

These data also provide the strongest evidence to date that HTLV-II, as well as HTLV-I, is associated with an array of predominantly motor and bladder neurologic findings. Although a limited number of studies have shown that HTLV-II–infected individuals are more likely than uninfected individuals to develop neurologic disability,[20] peripheral neuropathy,[21,22] and progressive myelopathy,[23] the role of HIV and/or drug-related factors could not be excluded. In this study, subjects were seronegative for HIV and only a small percentage reported injection drug use, which we adjusted for in our analysis. Although the role of HTLV-II in the development of neurologic disorders has been less clear than that of HTLV-I in the literature, our findings show similar odds of neurologic abnormalities across both groups of infected subjects. In addition, HTLV-II subjects had a significantly higher number of work-loss days compared with HTLV-seronegative subjects, even after adjusting for socioeconomic factors, which pro-

Figure 1 Survival to leg weakness (A), impaired gait (B), hyperreflexia in the lower limbs (C), impaired vibration sense (D), and urinary tract abnormality (E) by visit number and HTLV status



HTLV-I– and HTLV-II–infected subjects experienced lower survival to leg weakness, impaired gait, hyperreflexia, impaired vibration sense, and urinary tract abnormality compared with HTLV-seronegative subjects (log-rank $p < 0.01$ for all abnormality types). Neurologic examinations were not performed in visit 4.

vides support for increased morbidity, though not necessarily neurologic. HTLV-II subjects may have had more work-loss days as a result of their higher frequency of neurologic abnormalities or because of their higher incidence of respiratory tract infections and arthritis.[10] We have previously reported 4 cases of HAM among HTLV-II patients in the HOST cohort,[4] and there are a number of other HTLV-II HAM case reports in the literature.[28-34] These results, in addition to the spectrum of milder abnormalities found in our study, support the neuropathologic effects of this virus.

Our negative results on HTLV-I infection and peripheral sensory neuropathy contradict those of previous studies.[6-8,13] However, all but one of the studies consisted of uncontrolled case reports, so results could not be appropriately compared with HTLV-seronegative persons. Because peripheral neuropathy has multiple causes,[35] the use of a control group is critical. Confounding by other causes of peripheral neuropathy may account for some reports in the literature that lacked the kind of multivariate analysis we performed.

In contrast to our negative findings on impaired fine touch, we did find a higher incidence of impaired vibration sense among HTLV-I and -II subjects compared with seronegative subjects. Potential

Table 2 Crude and adjusted ORs and 95% CIs of neurologic signs and symptoms in HTLV-I– and HTLV-II–infected participants compared with HTLV-seronegative participants, visits 1–7*

Neurologic signs and symptoms	HTLV-seronegative (n = 810) n (%)†	HTLV-I (n = 153) n (%)†	HTLV-I (n = 153) OR‡ (95% CI)	HTLV-I (n = 153) ORa§ (95% CI)	HTLV-II (n = 388) n (%)†	HTLV-II (n = 388) OR‡ (95% CI)	HTLV-II (n = 388) ORa§ (95% CI)
Leg weakness	49 (6.0)	18 (11.8)	**1.73 (1.42–2.15)**	**1.67 (1.28–2.18)**	57 (14.7)	**1.53 (1.32–1.79)**	**1.44 (1.16–1.78)**
Gait abnormalities							
Impaired heel walking	88 (10.9)	24 (15.7)	**1.50 (1.26–1.79)**	**1.32 (1.07–1.65)**	89 (22.9)	**1.57 (1.38–1.78)**	**1.64 (1.39–1.93)**
Impaired toe walking	66 (8.1)	16 (10.4)	**1.39 (1.12–1.72)**	1.19 (0.90–1.57)	69 (17.8)	**1.61 (1.39–1.86)**	**1.73 (1.43–2.09)**
Impaired tandem gait	157 (19.4)	43 (28.1)	**1.41 (1.24–1.60)**	**1.25 (1.07–1.47)**	134 (34.5)	**1.41 (1.29–1.55)**	**1.45 (1.27–1.64)**
Reflex abnormalities							
Biceps hyperreflexia	26 (3.2)	7 (4.6)	1.16 (0.76–1.77)	1.15 (0.71–1.87)	6 (1.5)	0.76 (0.50–1.15)	0.49 (0.24–0.99)
Patellar hyperreflexia	70 (8.6)	16 (10.4)	1.17 (0.93–1.48)	1.28 (1.00–1.66)	42 (10.8)	1.14 (0.96–1.35)	0.99 (0.79–1.24)
Babinski sign	40 (4.9)	16 (10.4)	**1.49 (1.14–1.95)**	**1.54 (1.13–2.08)**	49 (12.6)	**1.61 (1.32–1.95)**	**1.51 (1.18–1.93)**
Sensory abnormalities							
Impaired sensation	26 (3.2)	8 (5.2)	**1.64 (1.17–2.30)**	1.49 (0.98–2.27)	23 (5.9)	**1.61 (1.24–2.10)**	1.34 (0.94–1.93)
Impaired vibration sense	277 (34.2)	67 (43.8)	**1.20 (1.07–1.34)**	**1.16 (1.01–1.33)**	174 (44.8)	**1.20 (1.11–1.31)**	**1.27 (1.14–1.42)**
Urinary tract abnormalities							
Prevoid urgency	146 (18.0)	41 (26.8)	**1.36 (1.20–1.53)**	**1.30 (1.12–1.49)**	118 (30.4)	**1.37 (1.26–1.50)**	**1.36 (1.22–1.52)**
Incontinence	105 (13.0)	33 (21.6)	**1.54 (1.34–1.78)**	**1.46 (1.23–1.72)**	110 (28.4)	**1.79 (1.62–1.97)**	**1.70 (1.50–1.93)**
Postvoid urgency	175 (21.6)	55 (35.9)	**1.52 (1.37–1.69)**	**1.47 (1.30–1.66)**	156 (40.2)	**1.51 (1.34–1.71)**	**1.61 (1.46–1.78)**

*Odds ratios (ORs) were derived from generalized estimating equations for repeated measures, and those in boldface type were significant at $p < 0.05$. ORs for impaired sensation were from visits 5–7.
†Cases represents number of cases who ever had an abnormality.
‡Crude OR. Models were adjusted for visit number and blood center.
§Adjusted OR (ORa). Models were adjusted for visit number, blood center, age at baseline, sex, race or ethnicity, educational attainment, alcohol and cigarette consumption, injection drug use, hepatitis C status, body mass index, and diabetes.
CI = confidence interval; HTLV = human T-lymphotropic virus.

age-related differences in vibration sensation between HTLV groups and seronegative subjects were excluded by multivariate analysis. Decreased vibration sense is among the main neurologic manifestations of HAM as defined by the World Health Organization,[36] but it has rarely been studied in HTLV-infected individuals without HAM. It is noteworthy that we found abnormality in vibration sense but not fine touch. The anatomy of spinal cord structures involved in advanced HAM is well known and includes the corticospinal tracts, anterior horn cells, and posterior columns.[37] The clinical findings among our subjects suggest that spinal cord involvement associated with HTLV-I or -II infection may affect single or multiple spinal cord structures across a clinical spectrum from asymptomatic to mild or severe involvement. Our data also suggest that peripheral sensory nerves are not a focus of HTLV neuropathology. The reasons for these sensory differences could be explored more fully in animal models.

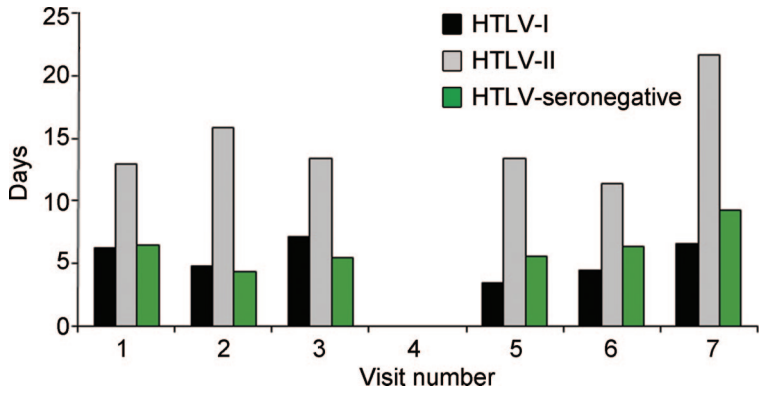
Table 3 Impaired sensation on monofilament examination by HTLV status and visit number*

	HTLV seronegative	HTLV-I	HLTV-II
Visit 5†	10 (1.9)	6 (6.6)	15 (5.9)
Visit 6‡	6 (1.1)	4 (4.3)	9 (3.5)
Visit 7	12 (0.8)	3 (3.8)	6 (2.9)

Data are presented as number (percentage).
*Monofilament examinations were not performed at visits 1–4. The χ^2 test was used to compare proportions; the Fisher exact test was used when n < 5. Denominators varied for each visit.
†$p = 0.009$ when comparing HTLV-I and HTLV-seronegative participants; $p = 0.003$ when comparing HTLV-II and HTLV-seronegative participants.
‡$p = 0.046$ when comparing HTLV-I and HTLV-seronegative participants; $p = 0.019$ when comparing HTLV-II and HTLV-seronegative participants.
HTLV = human T-lymphotropic virus.

Our current finding of a highly significant increased likelihood of prevoid and postvoid urgency and incontinence in both HTLV-I– and -II–infected subjects is consistent with other reports of HTLV-related neurogenic bladder in the literature, including our own.[10-12,38] Because we did not perform evaluations for urinary tract infections (UTI), it is conceivable that unrecognized UTI could account for our findings. However, a recent cross-sectional study of 157 HTLV-I–infected individuals found

Figure 2 **Self-reported mean number of work-loss days by HTLV status and visit number**



The mean number of work-loss days was greater at all visits for human T-lymphotropic virus (HTLV)-II subjects when compared with that for HTLV-I and HTLV-seronegative subjects ($p < 0.0001$). Neurologic examinations were not performed at visit 4.

that only 19% of 64 subjects with bladder symptoms had positive urine cultures, indicating that the majority of urinary symptoms were due to neurogenic bladder.[12] Furthermore, this study performed urodynamic studies on a subgroup of 21 symptomatic individuals with negative urine cultures and found evidence of neurogenic bladder in 81% of these individuals. These results argue that HTLV-I and -II subjects should have careful, periodic neurologic evaluation to document and symptomatically treat bladder as well as gait manifestations. Future prospective studies should include urodynamic evaluations and urine cultures.

Strengths of this study include its large sample size, prospective cohort design, standardized examinations, and long-term follow-up of both HTLV-infected and seronegative individuals. In addition, we conducted multivariate repeated-measures analyses to control for confounders that could obscure the relationship of HTLV with its neuropathologic features, although residual confounding may still have influenced the magnitude of the associations we observed. A potential weakness is the lack of blinding of participants and research nurses, which may have biased the association of HTLV infection and neurologic abnormalities upward. However, because our cohort consisted of voluntary blood donors, who are known to be healthier than the general population, it is likely that the absolute rates of neurologic abnormalities reported in our study are underestimates. Although we used rising from a chair without using the hands to screen for leg weakness, it is possible that balance, muscle, or joint abnormalities unrelated to motor function may explain difficulty in performing this maneuver.

Until longer follow-up of our cohort is achieved, it is difficult to speculate whether the neurologic abnormalities identified in subjects without HAM will remain stable or progress to a full diagnosis of HAM. Although our results suggest that some neurologic manifestations of HTLV-I and -II infection are isolated and do not reach the clinical threshold for the diagnosis of myelopathy, they remain consistent with the syndromic symptoms and signs of HAM. Our anecdotal data on abnormal neurologic examinations in 4 cohort participants who developed incident cases of HTLV-I or -II HAM further support the hypothesis that some participants with abnormal neurologic examinations will later progress to HAM.

Because only a small percentage of infected individuals develop HAM, HAM may simply be the "tip of the iceberg" of a broader spectrum of stable neurologic manifestations associated with HTLV infection.[39] This view is supported by recent clinical evidence of increased HTLV-I proviral loads, similar to those of HAM patients, in patients with neurologic abnormalities other than HAM compared with asymptomatic carriers.[40] These findings suggest that viral regulatory genes, genetic determination of the host's immunologic response, or both may be responsible for both HAM and the more subtle spectrum of neurologic abnormalities that we report. Virologic and immunologic studies of symptomatic non-HAM cases may help to clarify the etiology of HTLV neurologic outcomes.

AUTHOR CONTRIBUTIONS

Ms. Hope Biswas performed the statistical analysis and drafted the manuscript. Dr. John Engstrom provided neurologic expertise regarding the study measurements and analysis, and also critically reviewed the manuscript. Ms. Zhanna Kaidarova prepared the data for analysis and critically reviewed the manuscript. Drs. George Garratty, Joan Gibble, Bruce Newman, James Smith, and Alyssa Ziman conducted the study at its multiple centers and also critically reviewed the manuscript. Drs. Joy Fridey and Ronald Sacher both provided outcome adjudication and critically reviewed the manuscript. Dr. Edward Murphy designed the study and directed its implementation, including the study's analytic strategy, and assisted in drafting the manuscript.

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DISCLOSURE

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APPENDIX

The HTLV Outcomes Study (HOST) is the responsibility of the following persons:

Study Headquarters: University of California, San Francisco, CA: E.L. Murphy (Principal Investigator), J.W. Engstrom, D. DeVita, S. Yuen.

Blood Centers: American Red Cross Blood Services Greater Chesapeake and Potomac Region, Baltimore, MD: J.W. Gibble; American Red Cross Blood Services Southeastern Michigan Region, Detroit, MI: B.H. Newman; American Red Cross Blood Services Southern California Region, Pomona, CA: G. Garratty, A. Ziman, S.T. Hutching; Blood Centers of the Pacific, San Francisco, CA: M.P. Busch; Sylvan N. Goldman Center, Oklahoma Blood Institute, Oklahoma City, OK: J.W. Smith.

Central Laboratory: Blood Centers of the Pacific, San Francisco, CA: M.P. Busch, L. Pitina, L.H. Tobler.

Diagnostic Review Panel: E.L. Murphy, R.A. Sacher, J.L. Fridey.

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