

# Neurological Manifestations in Human T-Cell Lymphotropic Virus Type 1 (HTLV-1)-Infected Individuals Without HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis: A Longitudinal Cohort Study

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(See the Editorial Commentary by Taylor on pages 57–8.)

**Background.** Human T-cell lymphotropic virus type 1 (HTLV-1) is the agent of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), observed in up to 5% of infected individuals. Despite low prevalence, many HTLV-1-infected patients who do not fulfill criteria for HAM/TSP present with neurological complaints related to sensory, motor, urinary, or autonomic manifestations. The aim of this study was to determine the incidence of neurologic manifestations and risk factors associated with these outcomes.

**Methods.** The incidence of HAM/TSP and new signs and neurologic symptoms were computed in a group of patients enrolled in a cohort study.

**Results.** Of 414 subjects, 76 had definite HAM/TSP, 87 had possible or probable HAM/TSP, and 251 subjects had no neurologic manifestation and were selected for analysis. Definite HAM/TSP developed in 5 (1.47%) patients. Follow-up of at least 3 years was achieved in 51% of patients. The incidence rate was computed in 1000 person-years (206 for hand numbness, 187 for feet numbness, 130 for nocturia, and 127 for urgency). Average incidence rate in neurological exam was 76 for leg hyperreflexia, 53 for leg weakness, and 37 for Babinski sign. In the applied Expanded Disability Status Scale, the incidence rate of worsening 1 point was 134 per 1000 person-years. Kaplan–Meier curves stratified by sex and proviral load showed that females and patients with proviral load >50 000 copies/10<sup>6</sup> peripheral blood mononuclear cells had a higher risk of progression.

**Conclusions.** Development of neurological symptoms or signs occurred in up to 30% of asymptomatic subjects during 8 years of follow-up.

**Keywords.** HTLV-1; HAM/TSP; neurologic manifestations; cohort; incidence.

The human T-cell lymphotropic virus type 1 (HTLV-1) was the first human retrovirus described, initially found in a patient with cutaneous lymphoma [1]. Subsequently, the virus was also associated with an ancient neurological

condition called tropical spastic paraparesis (TSP) that was prevalent in Central America [2]. In Japan, a similar disease was found related to the virus and was called HTLV-1-associated myelopathy (HAM) [3]. After these

Received 26 August 2014; accepted 1 February 2015; electronically published 27 March 2015.

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**Clinical Infectious Diseases®** 2015;61(1):49–56

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DOI: 10.1093/cid/civ229

2 neurological conditions were found to be the same, an integrated name—HAM/TSP—was proposed to describe the entity [4].

HTLV-1 infects about 20 million people worldwide with a high prevalence in Japan, the Caribbean islands, Central and South America, and North and West Africa [5]. It is estimated that about 3%–5% of infected individuals develop myelopathy [6], but the annual incidence of HAM/TSP among HTLV-1-infected subjects is not well established. As classic clinical disease occurs mainly after the sixth decade, the incubation time has been considered to be in the range of 20–40 years [7].

Despite the low prevalence of HAM/TSP, HTLV-1-infected individuals can present with neurological or clinical symptoms related to the virus even without significant motor abnormalities (paraparesis). In cross-sectional studies comparing neurologic manifestations in HTLV-1-infected subjects who did not fulfill the criteria for diagnosis of HAM/TSP, numbness and weakness in the lower limbs, urinary symptoms of overactive bladder, erectile dysfunction, hyperreflexia in the lower limbs, and Babinski sign were found to be higher among HTLV-1 carriers than in seronegative individuals [8, 9].

Urinary manifestations are very common in HTLV-1 infection without HAM/TSP, with a reported prevalence that varies from 15% to 17% [8, 10]. In urodynamic studies, most of these alterations are due to detrusor overactivity and sphincter-detrusor dyssynergy [11]. Urinary symptoms may precede the diagnosis of HAM/TSP by years, suggesting that these symptoms may represent an oligosymptomatic manifestation of HAM/TSP [12].

There are few cohort studies in HTLV infection, and most are in patients with HAM/TSP [7, 13, 14]. Only 1 study followed up both HTLV-1- and HTLV-2-infected subjects without myelopathy and, although the incidence of urinary, motor, and sensory symptoms was high, none of the subjects developed definitive HAM/TSP [15]. The aim of this study was to determine the incidence rate of neurologic symptoms and signs in a cohort of HTLV-1-infected individuals without definitive HAM/TSP at baseline who were followed for up to 8 years.

## METHODS

This is a cohort study with 414 HTLV-1-infected individuals followed in the HTLV-1 clinic at Hospital Universitário Prof. Edgard Santos, Salvador, Bahia, Brazil. The period of study was from 2004 to 2011. HTLV-1 infection was diagnosed by detection of antibodies against viral antigens by enzyme-linked immunosorbent assay (ELISA) (Cambridge Biotech Corp, Worcester, Massachusetts) and confirmed by Western blot (HTLV blot 2.4, Genelab, Singapore). Subjects were referred mainly by blood banks at the time of attempted blood donation. Subjects were seen at 6- to 12-month intervals by a multidisciplinary team consisting of neurologists, urologists, rheumatologists, psychologists, and dentists. A standardized assessment was conducted each year with questions

about clinical, neurological, and urological symptoms. Physical and neurologic exams were also performed. Because of the complexity of coordinating multiple subspecialty visits, data for certain symptoms/signs were not available at each study visit.

## Case Definition

HAM/TSP diagnostic criteria were based on recommendations from an international consortium [16]. In brief, definite HAM/TSP is a nonremitting progressive spastic paraparesis with sufficiently impaired gait to be perceived by the patient. Sensory symptoms or signs may not be present but, when present, they are subtle and without a clear-cut sensory level. Urinary and anal sphincter signs or symptoms may or may not be present. Probable HAM/TSP was defined by a monosymptomatic presentation: spasticity or hyperreflexia in the lower limbs or isolated Babinski sign with or without subtle sensory signs or symptoms, or neurogenic bladder only confirmed by urodynamic tests. For both definite and probable definitions, clinicians must exclude an array of disorders that can mimic HAM/TSP. Possible HAM/TSP was defined by complete or incomplete clinical presentation in a setting where disorders resembling HAM/TSP have not been excluded. Anti-HTLV-1 antibodies in serum and/or cerebrospinal fluid are part of all of the above-mentioned criteria.

## Neurologic Evaluation

Muscular strength was evaluated with the Medical Research Council criteria [17] as follows: 0 = no muscular contraction; 1 = little contraction; 2 = active movement with no gravity; 3 = active movement against gravity; 4 = active movement against gravity and resistance; 5 = normal. Leg strength was evaluated on both sides in proximal and distal muscles. If the score was <4 in one muscle, the segment was considered weak for our analysis. Reflexes were defined according to the Campbell score [18]: 0 = none; 1 = present but diminished; 2 = normal; 3 = enhanced; 4 = hyperactive, with clonus. The routinely evaluated reflexes were biceps, triceps, brachioradialis in both arms, and patellar and ankle jerks in the legs. Any segment with a reflex graded 3 or 4 was considered abnormal. The time in seconds to walk 8 meters (m) was utilized in survival analysis, and increase in at least 10 seconds in time was the definition for failure. The Expanded Disability Status Scale (EDSS) scores [19] were computed each year. Sensory symptoms were self-reported (numbness, prickling, or tingling). These could be occasional or frequent and of any intensity, but they had to appear in the prior 12 months.

Overactive bladder syndrome was considered to be present if individuals had symptoms of urgency with or without incontinence, according to international criteria [20].

## Immunological Assays

Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized blood samples by density gradient

centrifugation using Ficoll-Hypaque. A total of  $3 \times 10^6$  cells/mL was cultured in RPMI 1640 supplemented with 2 mM L-glutamine, 25 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, 10% heat-inactivated fetal bovine serum, and 0.05% gentamicin. Cells were incubated only with medium for 72 hours at 37°C in 5% carbon dioxide. Determination of interferon gamma (IFN- $\gamma$ ) and tumor necrosis factor (TNF) levels in cell supernatants were performed by ELISA using reagents purchased from BD Bioscience Pharmingen (San Jose, California) as previously detailed [21].

### Proviral Load

The DNA was extracted from  $10^6$  PBMCs using proteinase K and salting-out procedure. HTLV-1 proviral load was determined using real-time TaqMan polymerase chain reaction method (Applied Biosystems) as described previously [22]. There is no consensus regarding the proviral load cutoff related to HAM/TSP. Some authors have used 1% (Furtado et al [23]) and 5% (Grassi et al [24]), corresponding to 10 000 or 50 000 copies per  $10^6$  cells, respectively. We chose the cutoff of 5%.

### Statistical Analysis

Survival analysis was performed with individuals without the symptom or sign at study entry as the at-risk population. Failure was defined as the development of the corresponding symptom or sign.

Censoring was applied to those lost to follow-up or who died of causes not related to HAM/TSP. Subjects were administratively censored on February 2012.

Kaplan–Meier curves were utilized to estimate the proportion without signs/symptoms, and the log-rank test was used to compare curves. Cox regression was performed to identify risk factors for neurologic worsening by EDSS score.

### Ethics

The ethical committee of the Federal University of Bahia and the Weill Cornell Medical College Institutional Review Board approved the study, and all participants provided written informed consent.

## RESULTS

Table 1 summarizes the baseline characteristics of the study participants. Of the 414 study subjects, 236 (59.2%) were referred from blood banks, 129 (32.3%) from other sources (television and radio advertisements, patient associations, and community associations), 17 (4.3%) from the neurology clinic, and 17 (4.3%) from family members. None of the patients referred from the neurology clinic were asymptomatic. Patients with definite HAM/TSP were older than subjects in the other groups, and no difference was found regarding sex. There was no difference regarding history of blood transfusion and intravenous drug use in the 3 groups.

**Table 1. Demographic and Epidemiologic Characteristics, Proviral Load, and Immunological Data of 414 HTLV-1–Infected Subjects, by Neurologic Status at Study Entry**

Characteristic	Without HAM/TSP (n = 251)	Probable or Possible HAM/TSP (n = 87)	HAM/TSP (n = 76)	P Value
Median age, y	44.6 $\pm$ 12.2	47.9 $\pm$ 11.6	52.4 $\pm$ 14.0	<.01 <sup>a</sup>
Female sex	143 (57.0)	58 (66.7)	51 (67.1)	.13 <sup>b</sup>
Breastfed as infant (n = 203)				.15 <sup>b</sup>
<1 y	72 (58.5)	24 (51.0)	17 (51.5)	
1–3 y	39 (31.7)	13 (27.7)	14 (42.4)	
>3 y	12 (9.8)	10 (21.3)	2 (6.1)	
Blood transfusion (n = 409)	38 (15.4)	22 (25.3)	16 (21.3)	.09 <sup>b</sup>
Intravenous drug use (n = 414)	8 (3.2)	4 (4.6)	2 (2.7)	.76 <sup>b</sup>
Homosexual activity (n = 285)	16 (8.9)	3 (5.5)	2 (4.0)	.27 <sup>b</sup>
HBV infection (n = 277)	14 (7.7)	8 (13.8)	2 (5.3)	.26 <sup>b</sup>
HCV infection (n = 276)	10 (5.7)	5 (8.5)	3 (7.5)	.65 <sup>b</sup>
Baseline proviral load (n = 251) <sup>c</sup>	25 109 (1924–79 234)	39 644 (3488–2701)	148 938 (84 465–278 815)	<.01 <sup>a</sup>
Baseline TNF- $\alpha$ (n = 257) <sup>d</sup>	209 (0–769)	346 (12–804)	719 (240–1574)	<.01 <sup>a</sup>
Baseline IFN- $\gamma$ (n = 257) <sup>d</sup>	866 (96–2036)	711 (45–1678)	2195 (773–3620)	<.01 <sup>a</sup>

Data are expressed as No. (%) unless otherwise specified.

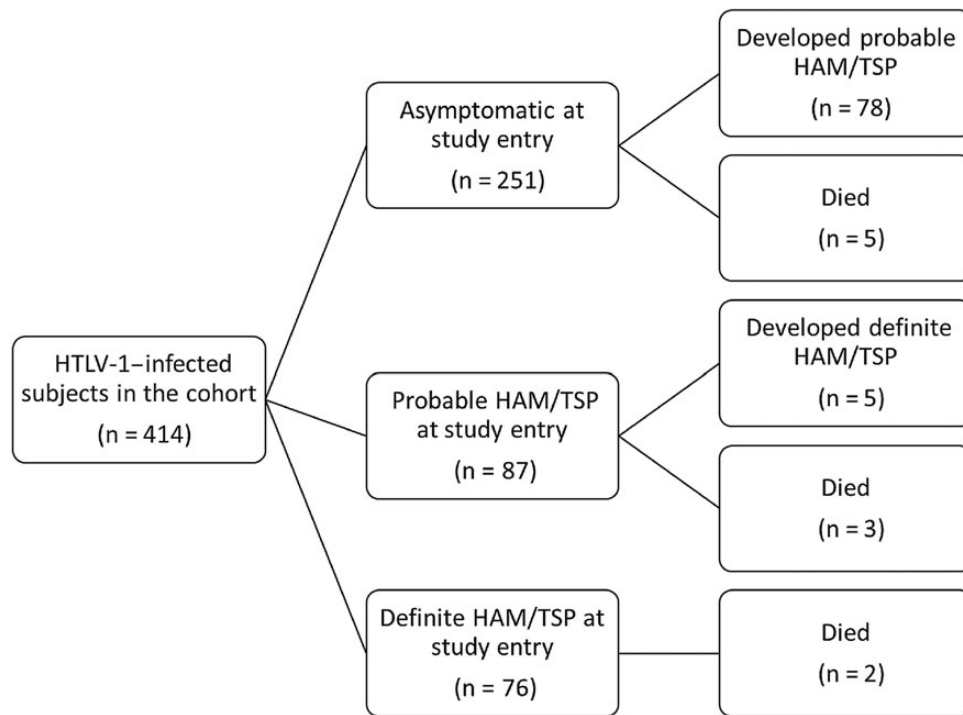
Abbreviations: HAM/TSP, HTLV-1–associated myelopathy/tropical spastic paraparesis; HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV-1, human T-cell lymphotropic virus type 1; IFN- $\gamma$ , interferon gamma; TNF- $\alpha$ , tumor necrosis factor alpha.

<sup>a</sup> One-way analysis of variance.

<sup>b</sup>  $\chi^2$  test.

<sup>c</sup> Expressed as number of HTLV-1 copies per  $10^6$  peripheral blood mononuclear cells, median (interquartile range).

<sup>d</sup> Expressed as pg/mL, median (interquartile range).



**Figure 1.** Outcomes of cohort participants. Abbreviations: HAM/TSP, human T-cell lymphotropic virus type 1–associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-cell lymphotropic virus type 1.

Figure 1 summarizes the outcomes of cohort participants. Of 414 HTLV-1–infected individuals evaluated, 76 had definite HAM/TSP (18.4%), 87 had possible or probable HAM/TSP (21%), and 251 (60.6%) patients did not have neurological disease related to HTLV-1 infection at study entry. During the study, 5 of 338 individuals (1.47%) without HAM/TSP at entry developed definite HAM/TSP. All of them had intermediate symptoms that were classified as probable HAM/TSP at entry, primarily neurogenic bladder confirmed by urodynamic study. In the group of asymptomatic individuals, 78 of 251 (31.07%) developed probable HAM/TSP.

Ten subjects died during follow-up of the following causes: 3 (30%) had acute T-cell lymphoma/leukemia (ATL), 2 (20%) other cancers, 2 (20%) myocardial infarction, 2 (20%) liver failure in the setting of hepatitis C virus (HCV) coinfection, and 1 (10%) accidental death (electrocution). Death rates were similar between the groups (Figure 1).

The asymptomatic group served as the study population for evaluating incident neurologic manifestations in subsequent analyses. From the sample of 251 carriers, 73.7%–100% did not have symptoms in the cohort at entry, depending on the variable analyzed, and 69.6%–75% had follow-up registered (Tables 2 and 3).

When self-reported symptoms were evaluated, sensory complaints had the highest annual incidence rates, computed in events per 1000 person-years: 206 for hand numbness and 187

for foot numbness. For urinary symptoms, nocturia had an incidence rate of 130, urgency of 127, retention 79, and incontinence 96. For motor symptoms, difficulty walking and difficulty running had incidence rates of 124 and 177, respectively (Table 2).

Among neurological signs, leg hyperreflexia had an incidence rate of 76 per 1000 person-years, followed by leg weakness (53), arm hyperreflexia (45), and Babinski sign (37). The incidence rate of increasing at least 1 point on the EDSS was 134 and 12 for increasing at least 20 seconds in an 8-m walk in the ambulatory index (Table 3).

The prevalence of symptoms described above did not differ significantly after stratification on baseline proviral load using a cutoff of 50 000 copies per  $10^6$  PBMCs and varied from 0.87%–24.4% in subjects with low proviral loads to 0%–26.9% in those with high proviral loads.

When Cox regression was applied using an EDSS increase of 1 point as the outcome, female sex and high proviral load ( $>50\,000$  copies/ $10^6$  PBMCs) were predictors of neurological worsening (hazard ratio [95% confidence interval], 1.80 [1.09–2.97],  $P = .02$  and 1.70 [.30–.98],  $P = .05$ , respectively). Other parameters including coinfections (hepatitis B virus, HCV, and syphilis) and comorbidities (hypertension, diabetes mellitus, and hypothyroidism) were not statistically significant. Of note, age was not associated with neurologic worsening or progression to definite HAM/TSP ( $P = .66$ ).

**Table 2. Survival Analysis of Self-Reported Symptoms in HTLV-1–Infected Subjects Without Human T-Cell Lymphotropic Virus Type 1 (HTLV-1)–Associated Myelopathy/Tropical Spastic Paraparesis**

Symptom	Initial Population Without Respective Symptom, no./No. (%)	Sample With Follow-up, no./No. (%)	Proportion of Failures, no./No. (%)	Median Person-time Observation, y (Max-Min)	Incidence Rate/1000 Person-years (95% Confidence Interval)
<b>Sensory symptoms</b>					
Hand numbness	173/251 (68.9)	129/173 (74.5)	73/129 (56.6)	2 (1–7)	206.2 (163–259)
Foot numbness	188/251 (73.7)	141/188 (75.0)	76/141 (53.9)	2 (1–7)	186.7 (149–233)
<b>Urinary symptoms</b>					
Nocturia	214/251 (85.2)	160/214 (74.7)	65/160 (40.6)	2 (1–7)	129.7 (101–165)
Urgency	251/251 (100)	187/251 (74.5)	73/187 (19.0)	2 (1–7)	126.9 (100–159)
Retention	238/251 (94.8)	178/238 (74.7)	50/178 (28.0)	3 (1–7)	79.1 (59–104)
Incontinence	226/251 (90.0)	169/226 (74.7)	69/169 (40.8)	5 (1–7)	95.8 (75–121)
<b>Motor symptoms</b>					
Difficulty walking	221/251 (88.0)	164/221 (74.2)	64/164 (39.0)	2 (1–7)	124.0 (97–158)
Difficulty running	215/251 (85.6)	159/215 (73.9)	77/159 (48.4)	2 (1–7)	177.4 (141–221)

Kaplan–Meier analyses demonstrated that women had a higher incidence of neurologic progression by EDSS, as did subjects with high baseline proviral loads (Figures 2 and 3). Moreover, there was no association between TNF and IFN- $\gamma$  production and neurologic progression (Supplementary Figure 1). The Kaplan–Meier adjusted incidences of neurologic manifestations showed that during up to 8 years of follow-up, the more common new symptoms and signs were (in decreasing frequency) leg paresthesias, urgency, incontinence, hyperreflexia, leg weakness, and Babinski sign (Supplementary Figure 2).

## DISCUSSION

HTLV-1 has been a neglected disease mainly due to the concept that it is a low-morbidity infection, as ATL and HAM/TSP are observed in <5% of infected subjects [25]. In this cohort study, we observed a high cumulative incidence of neurological

symptoms and signs of up to 56% of HTLV-1–infected individuals despite our low HAM/TSP rate. This indicates that despite the rarity of HAM/TSP, morbidity associated with HTLV-1 is high.

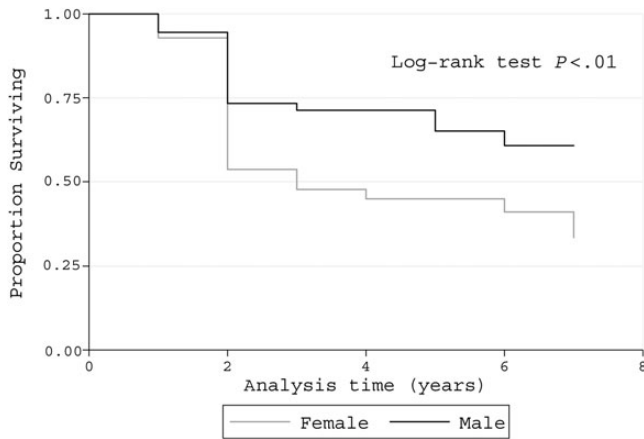
The appearance of symptoms in HTLV-1 patients seems to follow a particular order, beginning with mild sensorimotor manifestations (hyperreflexia/numbness) and urinary disturbances with evolution to leg weakness, and Babinski sign. Of the 5 patients who developed definite HAM/TSP in our cohort, all had urinary symptoms at study entry, mostly urgency with incontinence. All 5 patients had lower leg hyperreflexia (grade 3 or 4), none had leg weakness or Babinski sign, and all were considered to have probable HAM/TSP. The median time to onset of definite HAM/TSP was 4 years (range, 1–7 years).

Like the other HTLV cohort in non-HAM/TSP patients [15], our study showed a high incidence of symptoms. Moreover, our study calculated individual incidence rates and person-time at risk for each neurological symptom. Although we did not follow

**Table 3. Survival Analysis of Neurological Signs in Human T-Cell Lymphotropic Virus Type 1 (HTLV-1)–Infected Subjects Without HTLV-1–Associated Myelopathy/Tropical Spastic Paraparesis**

Sign	Initial Population Without Respective Symptom, no./No. (%)	Sample With Follow-up, no./No. (%)	Proportion of Failures, no./No. (%)	Median Person-time Observation, y (Max-Min)	Incidence Rate/1000 Person-years (95% CI)
<b>Neurological exam</b>					
Arm hyperreflexia	194/236 (82.2)	135/194 (69.6)	20/135 (14.8)	2 (1–7)	45.0 (30–72)
Leg hyperreflexia	198/244 (81.1)	148/198 (74.7)	34/148 (22.9)	2 (1–7)	75.8 (54–106)
Leg weakness	240/240 (100)	180/240 (75.0)	34/180 (18.8)	3 (1–7)	52.5 (37–73)
Babinski sign	243/243 (100)	181/243 (74.5)	25/181 (13.8)	3 (1–7)	36.6 (25–55)
<b>Neurological scales</b>					
EDSS	...	185/251 (73.7)	78/185 (42.1)	2 (1–7)	133.7 (107–167)
Delay in 10 s in walking 8 m	...	184/237 (77.6)	9/184 (4.8)	4 (1–7)	12.1 (6–23)

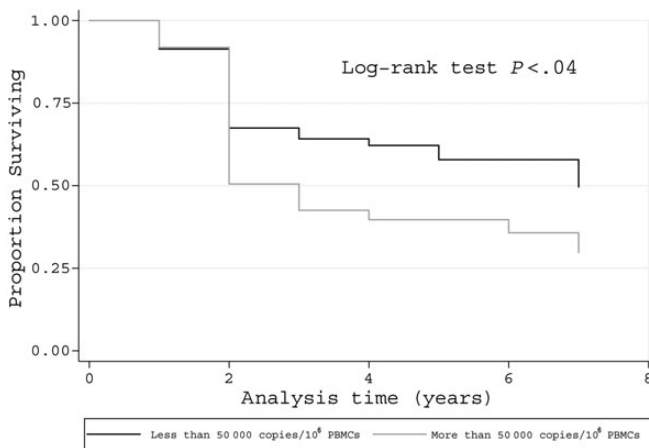
Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale.



**Figure 2.** Kaplan–Meier survival curve. Decrease in at least 1 point in Expanded Disability Status Scale in human T-cell lymphotropic virus type 1–asymptomatic individuals according to sex (n = 251).

a healthy control group to compare the incidence of symptoms and signs, the high rates and association of worsening neurological symptoms with high proviral load strongly suggest a causal relationship with HTLV-1 infection. Giving support to this finding, Biswas et al found that subjects with either HTLV-1 or HTLV-2 had higher prevalences of symptoms, especially involving the urinary and motor pyramidal systems, compared with healthy subjects [15].

The EDSS scale was designed for use in patients with multiple sclerosis [19]. However, it is useful for HTLV-1 infection because it can capture several neurologic domains including sensory, motor, and urinary. We have previously shown the association of EDSS with urinary manifestations, erectile



**Figure 3.** Kaplan–Meier survival curve. Decrease in at least 1 point in Expanded Disability Status Scale in human T-cell lymphotropic virus type 1–asymptomatic individuals according to proviral load (n = 130). Abbreviation: PBMCs, peripheral blood mononuclear cells.

dysfunction, and neurologic symptoms in HTLV-1 infection [10, 26, 27]. Our Cox regression analysis found 2 important risk factors at baseline for worsening EDSS—sex and HTLV-1 proviral load, both of which have been previously found to be associated with worsening neurological symptoms in patients with HTLV-1 without HAM/TSP [7, 13]. Neither age nor race was associated with neurologic progression in our study. The majority of our subjects (78%) were black or of mixed race and did not differ from whites with regard to progression, in keeping with literature data comparing blacks and whites [28].

In a previous study comparing neurologic symptoms and signs in HTLV-1 carriers and in uninfected individuals, complaints of difficulty walking were present in 11% of HTLV-1–infected subjects [8]. Here, although subjective complaints of difficulty walking were reported by >30% of the HTLV-1 carriers, objective determination by increased time to walk 8 m resulted in a lower incidence of gait difficulties. As prolongation of walking time was documented less frequently than leg weakness and hyperreflexia, and about as frequently as HAM/TSP itself, we may conclude that only severe pyramidal involvement appears to influence walking time.

Overactive bladder syndrome was found in at least 19% of the individuals, based on international criteria including the presence of urgency. Most of our patients were also evaluated with urodynamic studies, and detrusor overactivity was the most frequent finding. A prior study from our group showed that these urinary symptoms are not likely to be due to urinary tract infection [29]. We have recently shown that patients with overactive bladder have similar immunologic abnormalities and proviral load as patients with HAM/TSP and that production of proinflammatory cytokines (TNF- $\alpha$  and IFN- $\gamma$ ) and proviral load are higher than that observed in HTLV-1 carriers [30]. It is known that proviral load and production of proinflammatory cytokines are increased in patients with HAM/TSP and that these play a role in the pathogenesis of HTLV-1 infection [13, 31]. These data reinforce the concept that overactive bladder in these individuals is a manifestation related to HTLV-1. These symptoms have an important impact on the quality of life of these individuals.

There are multiple lines of evidence indicating that immunologic responses participate in the pathogenesis of diseases associated with HTLV-1. Children with infective dermatitis, a disease that is recognized as a risk factor for HAM/TSP, have high production of proinflammatory cytokines [32]. Furthermore, patients with periodontal disease associated with HTLV-1 have increased expression of proinflammatory cytokines and a decrease in regulatory T cells and the regulatory cytokine interleukin 10 (IL-10) [31]. Here we evaluated if the production of TNF- $\alpha$  and IFN- $\gamma$  at entry in the study was associated with development of neurologic symptoms. Our cytokine analysis did not show statistically significant differences between high and low producer groups in Kaplan–Meier curves;

there was a trend, however, for an association between high TNF- $\alpha$  levels and neurologic progression ( $P = .07$ ). Recent data have suggested that impaired ability of regulatory cytokines such as IL-10 and TGF- $\beta$  to downregulate the inflammatory response may be a better marker for development of HAM/TSP than proinflammatory cytokine production per se [30].

Of note, whereas 19% of HTLV-1 carriers in our cohort developed overactive bladder, only 1.47% developed HAM/TSP. At study entry, 62 HTLV-1-infected individuals already had overactive bladder, but only 3 of them developed definitive HAM/TSP. Taken together, these data suggest that the majority of HTLV-1-infected subjects with overactive bladder do not progress to HAM/TSP in the short term, indicating that in addition to the exaggerated production of proinflammatory cytokine and high proviral load, other factors participate in the development of HAM/TSP. The cumulative incidence of HAM/TSP in our study (1.47%) was less than that found in the literature (3%–5%), but the duration of follow-up (maximum 8 years) was too short compared with the historic average time of 20 years to develop the disease [7].

Regarding ATL development, very few patients in our cohort had the disease (3 patients, all of whom died). Two had histories of relapsing strongyloidiasis, a condition that is associated with ATL [33]. The other patient had HAM/TSP and developed ATL during follow-up. Although this sequence is uncommon, it has been reported in Brazil [34].

Our study has several noteworthy strengths and limitations. The relatively large sample size and comprehensive multidisciplinary evaluations of study subjects are key strengths. The duration of follow-up, however, is short relative to the prolonged natural history of HTLV-1 infection. Furthermore, our findings may not be generalizable to other geographic regions and are limited by potential selection biases related to which patients are referred to and continue to be followed at an academic center. Given that a substantial proportion of study subjects were asymptomatic blood donors found to be HTLV-1 infected at the time of attempted donation, the potential for bias is somewhat reduced.

In conclusion, the findings of this clinic-based cohort study show that HTLV-1-infected individuals had high rates of developing neurologic symptoms and signs, especially involving the sensory, urinary, and motor tracts. These findings have the potential to adversely affect quality of life in patients with HTLV-1 infection. Moreover, although there is no established therapy for HAM/TSP, symptomatic treatment of these manifestations may improve quality of life and the ability to work.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted

materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

**Disclaimer.** The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health (NIH).

**Financial support.** This work was supported by the National Council of Technological and Scientific Development and the US NIH (grant number R01 AI079238).

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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