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Original Research

Evolution of erectile dysfunction in individuals infected with human T-lymphotropic virus 1: a prospective cohort study

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Abstract

Background: Virtually all patients with human T-lymphotropic virus 1 (HTLV-1)–associated myelopathy/tropical spastic paraparesis (HAM/TSP) have some degree of erectile dysfunction (ED), but ED is also found in a large percentage of HTLV-1 carriers.

Aim: To evaluate the evolution of ED in individuals infected with HTLV-1 who were followed for up to 15 years.

Methods: This prospective cohort study included men infected with HTLV-1 who had ED, were aged 18 to 70 years, and were followed from January 2004 to December 2019. We used the International Index of Erectile Function–5 (IIEF-5), the Expanded Disability Status Scale and Osame Motor Disability Scale, and the Overactive Bladder Symptom Score (OABSS) to define and stratify ED, neurologic disability, and bladder dysfunction, respectively.

Outcomes: Time to development of severe ED was the main outcome.

Results: We studied 90 men with ED (mean ± SD age, 52.8 ± 9.78 years). At baseline, 42 were carriers, 16 had probable HAM/TSP, and 32 had definite HAM/TSP. IIEF-5 was highest among carriers and lowest in patients with definite HAM/TSP, whereas OABSS was lowest in carriers and highest in patients with definite HAM/TSP. Median (IQR) follow-up was 8.50 years (3.00-12.00). IIEF-5 fell significantly from baseline to last follow-up among carriers and patients with probable and definite HAM/TSP. There was an inverse correlation between the IIEF-5 and the OABSS at last follow-up ($r = -0.62$, $P < .001$). In survival analysis, the time to development of severe ED was significantly shorter in patients with definite HAM/TSP when compared with carriers ($P = .001$) and those with probable HAM/TSP ($P = .014$). The presence of definite HAM/TSP at baseline was independently associated with the development of severe ED, after adjustment for baseline age and proviral load (hazard ratio, 6.74; $P = .008$).

Clinical Implications: Formal assessment of erectile function should be part of the routine clinical assessment of individuals infected with HTLV-1; worsening erectile function should alert clinicians to the possibility of neurologic deterioration.

Strengths and Limitations: This is the first prospective cohort study to describe the course of ED in men infected with HTLV-1. The small sample size and absence of seronegative controls are limitations.

Conclusion: ED is a slowly progressive clinical manifestation of HTLV-1 infection, and the degree of neurologic compromise at baseline is the main predictor of time to progression to severe ED.

Keywords: erectile dysfunction; human T-lymphotropic virus 1; neurologic disease; cohort.

Introduction

Human T-lymphotropic virus 1 (HTLV-1) is the etiologic agent of HTLV-1–related disease[1] and is endemic in Africa, the Caribbean, South America, and Japan.[2] HTLV-1 is associated with low mortality rates, but morbidity might be quite significant, especially in patients who develop HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) or adult T-cell leukemia/lymphoma.[1,3] Less severe manifestations of HTLV-1 infection are more common, such as arthropathy, myositis, periodontitis, uveitis, dry syndrome, lower urinary tract symptoms, and erectile dysfunction (ED).[4–6]

Definite HAM/TSP is characterized by low back pain, paresthesia and weakness of the lower limbs, spastic paraparesis, and inability to walk.[3,7] Individuals infected with HTLV-1 who do not have motor impairment but present with symptoms such as urinary dysfunction are considered as having probable HAM/TSP.[7] More than half of those infected with HTLV-1 have some urologic manifestation; the most common is overactive bladder, occurring in 62% of patients with urinary complaints and characterized by increased urinary frequency, nocturia, urgency, and urinary incontinence.[8] Some patients may also present with a flaccid bladder associated with a weak urinary stream and voiding effort, incomplete bladder emptying, and urinary retention.[9,10] There is a strong association between urinary dysfunction and ED. For example, it has been shown that

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ED is much more common in patients with HTLV-1 who have a neurogenic bladder (79%) than in those who do not (39%).[11,12]

Few studies have addressed the occurrence of ED in individuals infected with HTLV-1, and its pathophysiology needs further clarification. It is known that ED is more common in individuals with HTLV-1 than in seronegative controls.[5,11] In the HTVL-1 population, the presence of neurologic impairment is the greatest risk factor for ED; traditional risk factors, such as arterial hypertension, diabetes mellitus, dyslipidemia, obesity, anxiety, and depression, appear to play a lesser role.[13,14] However, young patients infected with HTLV-1 may have ED without overt neurologic symptoms.[12] Collectively, these data suggest that the pathophysiology of ED in those infected with HTLV-1 might be more neurologic than vascular in nature and that worsening erectile function might be a precursor to bladder and motor impairment.

Based on the International Index of Erectile Function–5 (IIEF-5), ED in HTLV-1 infection ranges from mild to severe.[15] There is a lack of studies evaluating the evolution of ED and its relationship with the progression of urinary and motor manifestations. The aim of this study was to evaluate the evolution of ED in individuals infected with HTLV-1.

Methods

Study design and population

The current cohort study was carried out at the HTLV-1 multidisciplinary outpatient clinic of the University Hospital of the Federal University of Bahia (Bahia, Brazil). Data were acquired between January 2004 and December 2019. Inclusion criteria were as follows: a positive enzyme-linked immunosorbent assay test result for HTVL-1 confirmed by Western blot and an IIEF-5 score <22. Exclusion criteria were history of cancer, psychiatric disorders, use of penile prosthesis, motor deficit caused by other neurologic disorders, and age <18 or >70 years. Patients were followed at least once a year for a minimum of 3 years until December 2019 or until they were 70 years old.

ED assessment

The IIEF-5 is a self-administered questionnaire with a scale ranging from 5 to 25.[15] The 5 questions revolve around confidence, quality of erections, and satisfaction with intercourse. Patients were asked to respond to questions considering their sexual performance when they are not taking medications for ED, such as phosphodiesterase inhibitors. IIEF-5 values <22 are compatible with ED: 17 to 21, mild; 12 to 16, mild to moderate; 8 to 11, moderate; and 5 to 7, severe. Data were recorded at study entry and once a year until the patient's last visit.

Clinical form

History and physical examination, including neurologic, were performed on all participants. Osame Motor Disability Score (OMDS)[3] and Expanded Disability Status Scale (EDSS)[7] were applied to assess the presence and degree of motor disability. Patients were classified as carriers, probable HAM/TSP, and definite HAM/TSP based on the de Castro-Costa criteria.[7] Patients with ODMS >1 and/or EDSS ≥2 were diagnosed as definite HAM/TSP. Patients with ODMS ≤1 and EDSS ≥0 and <2 were considered to have probable HAM/TSP. HTLV-1 carriers were seropositive individuals without symptoms or signs of neurologic disease; they had EDSS and ODMS equal to 0. Neurologic assessment was performed at the beginning of the cohort and annually until the end of follow-up.

Overactive bladder assessment

The Overactive Bladder Symptom Score (OABSS) was used to assess bladder dysfunction.[16] The OABSS is a 4-question questionnaire on urinary symptoms: daytime frequency (2 points), nighttime frequency (3 points), urgency (5 points), and urgency incontinence (5 points). The score represents the sum and ranges from 0 (absence of urinary symptoms) to 15.

Assessment of proviral load

DNA were extracted from 10^6 peripheral blood mononuclear cells (PBMCs) with proteinase K and the salting-out method. HTLV-1 proviral load was quantified with a TaqMan real-time polymerase chain reaction assay as described previously with the ABI Prism 7700 Sequence Detection System (Applied Biosystems).[17] Albumin DNA was used as an endogenous reference. The normalized value of HTLV-1 proviral load was calculated as the ratio of the mean number of HTLV-1 DNA copies over the number of albumin DNA copies $\times 2 \times 10^6$ and expressed as the number of copies of HTLV-1 $\times 10^6$ PBMCs.

Risk factors for progression to severe ED

The main risk factors for progression to severe ED evaluated in this study were age, proviral load at baseline, and degree of neurologic impairment (EDSS score) at baseline. Additional analyses were performed including variables related to metabolic syndrome (hypertension, diabetes, body mass index, abdominal girth, total cholesterol, glucose, and triglyceride levels), as well as hormonal factors (luteinizing hormone, follicle-stimulating hormone, prolactin, and total testosterone levels) and psychogenic factors (anxiety and depression scale). These variables were obtained from databases used in 2 previously published studies by our group[13,14]; since those studies, we have not been systematically measuring and recording these variables. Therefore, we have approximately 50% missing data for these complementary analyses.

Ethical issues

The Institutional Review Board of the Medical School of Bahia of the Federal University of Bahia approved the study protocol. All patients provided written informed consent.

Statistical analysis

The Kolmogorov-Smirnoff test was used to evaluate the distribution of numeric variables. Normally distributed variables were presented as mean ± SD and nonnormally distributed as median (IQR). Categorical variables were presented as absolute and relative frequencies. One-way analysis of variance for independent samples and Kruskal-Wallis test were used to compare normally and nonnormally distributed numeric variables among 3 groups, respectively; appropriate post hoc tests were used for pairwise multiple comparisons after analysis of variance and Kruskal-Wallis. Paired comparisons of IIEF-5 at baseline and last follow-up were performed with the Wilcoxon signed rank test. Spearman correlation coefficient was used to summarize the correlation between OABSS and IIEF-5 at last follow-up. The chi-square and Fisher exact tests were used to compare categorical variables. Survival analyses

Table 1. Demographic and clinical features of 90 men who were infected with HTLV-1 and had erectile dysfunction according to the clinical form of the infection at baseline.[a]

Variable	Carriers	Probable HAM/TSP	Definite HAM/TSP	*P* value[b]
Men, No. (%)	42 (46.7)	16 (17.8)	32 (35.6)	
Age,[c] y, mean ± SD	50.2 ± 9.32	57.1 ± 7.45	54.0 ± 10.60	.035
IIEF-5[d]	18.0 (15.0-21.0)	15.0 (11.5-16.0)	10.0 (7.25-15.75)	<.001
OABSS[e]	0.0 (0.0-0.0)	5.0 (4.0-6.75)	7.0 (6.0-9.0)	<.001
Proviral load,[f] copies × 10^6 PBMCs	16 053 (1623-71 629)	119 821 (25 315-305 929)	141 654 (18 098-250 711)	.007
Follow-up, y	6.5 (4.0-12.0)	8.50 (5.0-12.75)	9.0 (5.0-12.0)	.761

Abbreviations: HAM/TSP, HTLV-1–associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-lymphotropic virus 1; IIEF-5, International Index of Erectile Dysfunction 5; OABSS, Overactive Bladder Symptom Score; PBMCs, peripheral blood mononuclear cells. [a]Data are presented as median (IQR) unless noted otherwise. [b]*P* value obtained with analysis of variance (age) and Kruskal-Wallis (all other variables) and reflects the comparison among the 3 groups; pairwise comparisons were performed through post hoc tests for analysis of variance and Kruskal-Wallis tests. [c]Age was significantly different between carriers and probable HAM/TSP ($P = .047$). [d]IIEF-5 was significantly different between carriers and probable HAM/TSP ($P = .026$) and carriers and definite HAM/TSP ($P < .001$), but the difference between probable and definite HAM/TSP was marginal ($P = .086$). [e]All pairwise comparisons were statistically significant for OABSS ($P < .001$ for carriers vs probable HAM/TSP and for carriers vs definite HAM/TSP; $P = .044$ for probable vs definite HAM/TSP). [f]Proviral load was significantly different between carriers and definite HAM/TSP ($P = .006$) and between carriers and probable HAM/TSP ($P = .014$) but not different between probable and definite HAM/TSP ($P = .746$).

were conducted via the Kaplan-Meier method to evaluate the time to development of severe ED, and the comparison of curves was performed with the log rank test. Univariate and multivariate Cox proportional hazards regression was used to assess the effect of age and proviral load on the time to development of severe ED. Additional analyses were conducted evaluating the effect of variables related to metabolic syndrome and hormonal and psychogenic factors on development of severe ED; these complementary analyses were limited by approximately 50% missing data. A *P* value <.05 in final analyses was considered statistically significant. All analyses were conducted with SPSS Statistics version 20 (IBM) except for the box plot, which was constructed with Stata version 12.1 (StataCorp).

Results

We screened 121 men with ED who were followed at the HTLV-1 outpatient clinic; 31 were excluded from this study for the following reasons: lack of follow-up (n = 13), age >70 years (n = 12), history of cancer (n = 2), use of penile prosthesis (n = 2), sequelae of poliomyelitis (n = 1), and sickle cell anemia (n = 1). The remaining 90 men with ED were included in the final analyses.

Table 1 presents the demographic and clinical characteristics of the participants stratified by clinical form at baseline. Carriers represented 46.7% of the sample; 17.8% had probable HAM/TSP and 35.6% definite HAM/TSP. The mean age of the patients was 52.8 ± 9.78 years. Patients with probable HAM/TSP were significantly older than carriers ($P = .047$). The median IIEF-5 for the entire sample was 15.0 (11.0-18.25). IIEF-5 was highest in carriers and lowest in patients with definite HAM/TSP. The median OABSS for the sample was 4.0 (0.0-7.0); the lowest scores were found in carriers and the highest in patients with definite HAM/TSP. The median proviral load for the sample was 48 718 copies (2327-201 981) × 10^6 PBMCs; the highest values were observed among patients with probable HAM/TSP and the lowest among carriers. Patients were followed for a median 8.50 years (3.00-12.00); length of follow-up was not different across groups.

Table 2 shows the degree of ED at baseline and last follow-up stratified by clinical form at baseline. Among carriers, 7 patients experienced worsening erectile function during follow-up and progressed from mild ED to mild/moderate (n = 2), moderate (n = 2), and severe (n = 3). Both carriers who progressed to moderate ED also experienced progression of their clinical form to probable HAM/TSP (data not shown).

Of the 3 carriers who progressed to severe ED, 2 advanced to definite HAM/TSP, and 1 remained a carrier (data not shown). In the probable HAM/TSP group, 3 patients progressed from mild to mild/moderate ED. In the definite HAM/TSP group, 10 patients went on to more advanced forms of ED; at last follow-up, 46.9% of patients with HAM/TSP had severe ED, and only 3.1% had mild ED.

This decline in erectile function is illustrated in Figure 1; it shows the IIEF-5 at baseline and last follow-up across the 3 clinical forms. IIEF-5 fell significantly from baseline to last follow-up among carriers (median fall, 2.0; $P < .001$), probable HAM/TSP (median fall, 3.0; $P = .016$), and definite HAM/TSP (median fall, 2.0; $P < .001$).

Figure 2 shows a moderate inverse correlation between the OABSS at last follow-up and the IIEF-5 at last follow-up (Spearman rho = −0.62, $P < .001$), indicating that patients with more urinary symptoms had worse erectile function.

Figure 3 shows the Kaplan-Meier survival analysis of time to development of severe ED. Ten patients (2 with probable HAM/TSP and 8 with definite HAM/TSP) were excluded from this analysis because they already had severe ED at baseline. Time to event was significantly faster in patients with definite HAM/TSP when compared with carriers ($P = .001$) and probable HAM/TSP ($P = .014$); there was no significant difference in time to event between carriers and probable HAM/TSP ($P = .307$).

Next, we conducted multivariate Cox proportional hazards regression analyses to evaluate if the degree of neurologic involvement at baseline was an independent predictor of progression to severe ED. These analyses were also conducted on 80 patients, as 10 patients already had severe ED at baseline. In the first model, we used the EDSS score as a continuous variable to represent the degree of neurologic involvement at baseline (our main independent variable). As shown in Table 3 (model 1), the EDSS score was independently associated with the development of severe ED, after adjustment for age and proviral load at baseline. For each unit increase in baseline EDSS score, there was a 1.35 increase in the odds of severe ED ($P = .038$). In the second model, we categorized the baseline EDSS into definite HAM/TSP and others (a combination of carriers and probable HAM/TSP). As shown in Table 3

Table 2. Degree of ED at baseline and last follow-up in 90 individuals infected with HTLV-1 stratified by clinical form at baseline.[a]

Degree of ED	Carriers (n = 42)		Probable HAM/TSP (n = 16)		Definite HAM/TSP (n = 32)	
	Baseline	Last follow-up	Baseline	Last follow-up	Baseline	Last follow-up
Mild	25 (59.5)	18 (42.9)	3 (18.8)	3 (18.8)	6 (18.8)	1 (3.1)
Mild/moderate	14 (33.3)	16 (38.1)	9 (56.2)	6 (37.5)	9 (28.1)	4 (12.5)
Moderate	3 (7.1)	5 (11.9)	2 (12.5)	5 (31.2)	9 (28.1)	12 (37.5)
Severe	0 (0.0)	3 (7.1)	2 (12.5)	2 (12.5)	8 (25.0)	15 (46.9)

Abbreviations: ED, erectile dysfunction; HAM/TSP, HTLV-associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-lymphotropic virus 1. [a] Data are presented as No. (%).

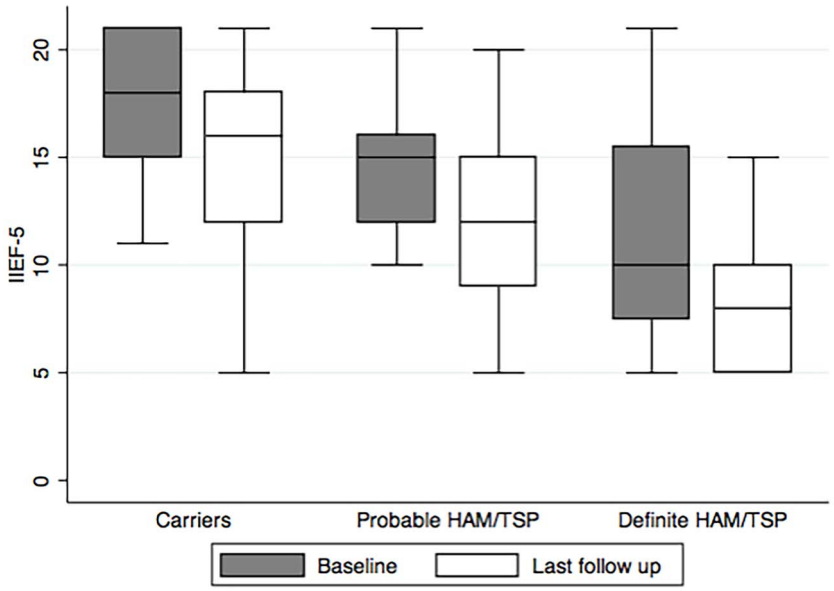

Figure 1. Median IIEF-5 at baseline and last follow-up in 90 individuals infected with HTLV-1 stratified by clinical form at cohort entry. Box plot represents IIEF-5 at baseline (black) and last follow-up (white). Intragroup comparisons were performed with the Wilcoxon signed rank test. IIEF-5 fell significantly from baseline to last follow-up among carriers ($P < .001$), probable HAM/TSP ($P = .016$), and definite HAM/TSP ($P < .001$). Across-group comparisons of the IIEF-5 were performed with the Kruskal-Wallis test. There was a significant difference in IIEF-5 values across groups at baseline ($P < .001$) and last follow-up ($P < .001$). Post hoc multiple comparisons were performed to identify pairwise differences. At baseline, carriers had higher IIEF-5 than probable HAM/TSP ($P = .026$) and definite HAM/TSP ($P < .001$); the difference between probable and definite HAM/TSP was not statistically significant ($P = .086$). At last follow-up, carriers had marginally higher IIEF-5 than probable HAM/TSP ($P = .058$) and significantly higher IIEF-5 than definite HAM/TSP ($P < .001$); IIEF-5 was also significantly higher in probable HAM/TSP than in definite HAM/TSP ($P = .012$). HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-lymphotropic virus 1; IIEF-5, International Index of Erectile Function–5.

(model 2), the presence of definite HAM/TSP at baseline was independently associated with the development of severe ED, after adjustment for baseline age and proviral load. The odds of progressing to severe ED was 6.74 times greater in patients with definite HAM/TSP when compared with carriers and probable HAM/TSP combined ($P = .008$). Figure 4 presents this second multivariate Cox proportional hazards regression model.

Finally, we sought to adjust the effect of the degree of neurologic involvement at baseline on progression to severe ED for the influence of variables related to metabolic syndrome (hypertension, diabetes, abdominal girth, body mass index, serum glucose, and lipids), hormonal factors (luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin), and psychogenic factors (anxiety and depression); unfortunately, we had these data for approximately 50% of our sample. In univariate Cox proportional hazards analyses, baseline EDSS (n = 80), abdominal girth (n = 46), and anxiety (n = 43) and depression (n = 43) scores were significantly associated with progression to severe ED. These 4 variables were included in a stepwise, backward, multivariate Cox proportional hazards regression model (n = 39, 51.2% missing data). In the end, only baseline EDSS remained independently associated with progression to severe ED (hazard ratio, 1.852 [95% CI, 1.187-2.890]; $P = .007$).

Discussion

In the HTLV-1 literature, ED was initially described as a clinical finding in a case report.[18] Several reports have accumulated since. More recently, our group has shown an association between ED and HTLV-1–induced urinary/motor dysfunction.[11] Furthermore, it has become increasingly clear that a large percentage of HTLV-1 carriers may also develop ED.[4,5,12] Most studies on ED in this population are cross-sectional or case series; to our knowledge, no long-term longitudinal studies focusing on ED in individuals infected with HTLV-1 have been reported. In this prospective cohort with up to 15 years of follow-up, we confirmed that severe ED is more common in patients with definite HAM/TSP but can be observed in patients with probable HAM/TSP and carriers.

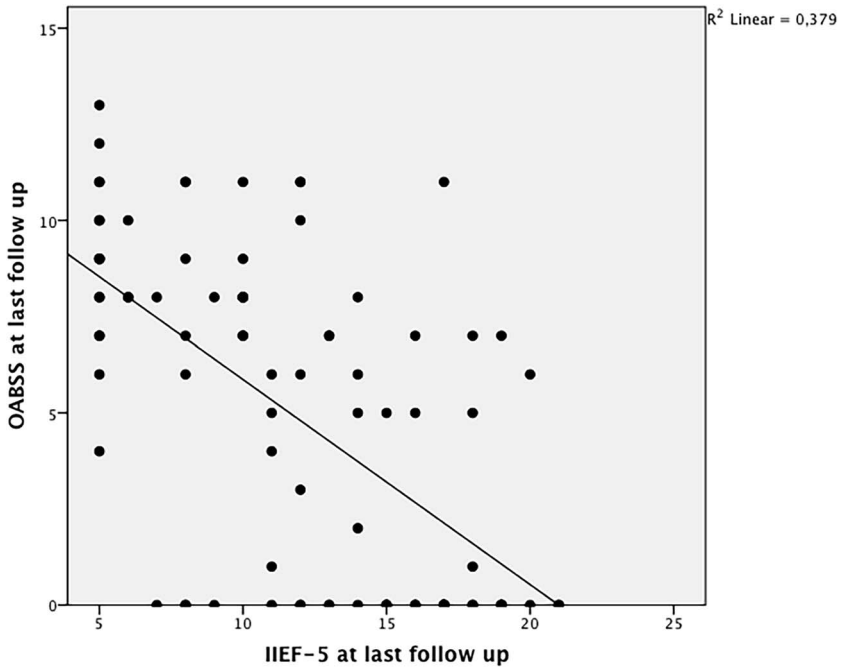

Figure 2. Linear bivariate correlation between IIEF-5 and OABSS at last follow-up in men infected with HTLV-1 who had erectile dysfunction: Spearman correlation coefficient = −0.62, $P < .001$. IIEF-5, International Index of Erectile Function–5; OABSS, Overactive Bladder Symptom Score.

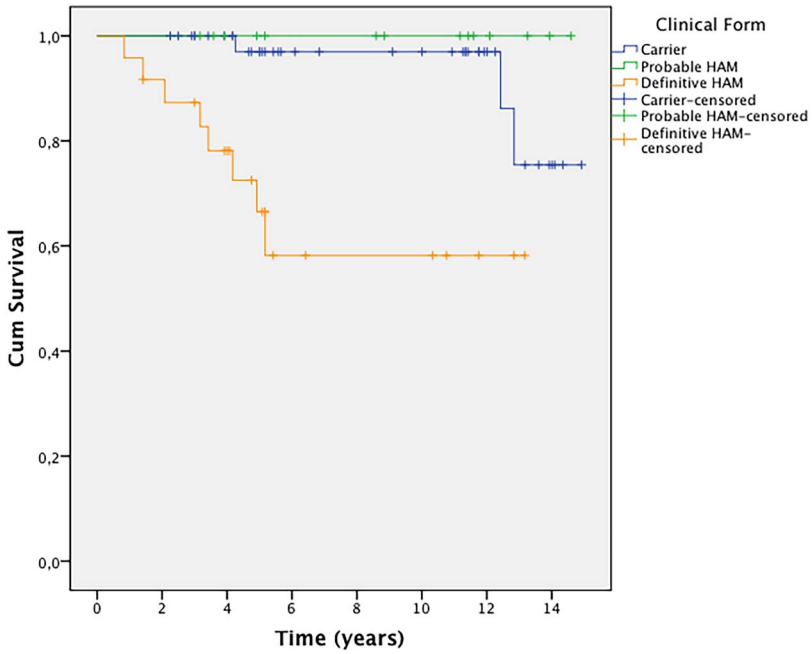

Figure 3. Time to development of severe erectile dysfunction among patients infected with HTLV-1 stratified by clinical form at baseline. Ten patients (2 with probable HAM/TSP and 8 with definite HAM/TSP) were excluded from this analysis because they already had severe erectile dysfunction at baseline. There was no significant difference in time to event between carriers and probable HAM/TSP ($P = .307$), but there were significant differences between carriers and definite HAM/TSP ($P = .001$) and between probable and definite HAM/TSP ($P = .014$). All comparisons were made via the log rank test. HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-lymphotropic virus 1.

We additionally found that progression to severe ED is faster in patients with HAM/TSP than in patients with less severe neurologic involvement or carriers. IIEF-5 values were higher in carriers than in those with probable and definite HAM/TSP, showing that ED is more severe in symptomatic HTLV-1.

Age is one of the main risk factors for ED in the general population. In patients with HTLV-1, age and the presence of motor or urinary dysfunction are independent risk factors for ED.[11,12] Nevertheless, ED can be detected in young men infected with HTLV-1.[11]

An important finding of this study was that almost half the participants who had ED were in the carrier group and hence did not have any detectable neurologic involvement. It is known that psychogenic factors play an important role in ED; therefore, as this study was carried out in an HTLV-1 outpatient clinic, we cannot rule out that the presence of patients

Table 3. Multivariate Cox proportional hazards regression analyses evaluating the degree neurologic involvement at baseline as an independent predictor of progression to severe ED.

Variables at baseline	Progression to severe ED	*P* value
	HR (95% CI)	
Model 1: neurologic involvement as a continuous variable (EDSS score)		
Baseline EDSS score	1.35 (1.02 to 1.79	0.038
Age	1.00 (0.93 to 1.07	0.963
Proviral Load	1.00 (1.00 to 1.00	0.891
Model 2: neurologic involvement as a categorical variable (definite vs probable HAM/TSP + carriers)		
Definite HAM/TSP	6.74 (1.66 to 27.3)	0.008
Age	0.99 (0.93 to 1.06)	0.826
Proviral Load	1.00 (1.00 to 1.00)	0.989

Abbreviations: ED, erectile dysfunction; EDSS, Expanded Disability Status Scale; HAM/TSP, HTLV-associated myelopathy/tropical spastic paraparesis; HR, hazard ratio; HTLV-1, human T-lymphotropic virus 1.

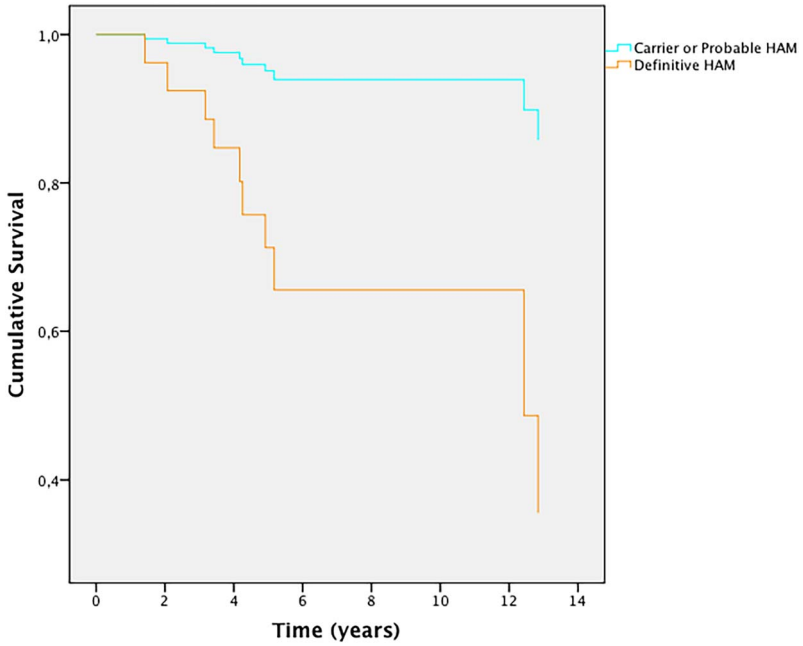

Figure 4. Time to development of severe erectile dysfunction among patients infected with HTLV-1, stratified by carrier or probable and definite HAM/TSP and adjusted for baseline age and proviral load. Ten patients (2 with probable and 8 with definite HAM/TSP) were excluded from this analysis because they already had severe erectile dysfunction at baseline. The time to development of severe erectile dysfunction was significantly faster in patients with definite HAM/TSP when compared with all others (carriers + probable HAM/TSP), even after adjustment for age and baseline viral load. HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-lymphotropic virus 1.

in wheelchairs or with other neurologic manifestations, in the same environment, may have influenced the high frequency of ED among HTLV-1 carriers. However, we previously showed that the psychogenic factor did not increase the risk for ED in individuals infected with HTLV-1.[14]

Urinary dysfunction, mainly characterized by overactive bladder, is observed in a large percentage of individuals infected with HTLV-1, and there is a strong association between urinary dysfunction and ED in HTLV-1 infection.[11,12] The OABSS is widely used to assess the degree of voiding symptoms, and here we observe an inverse correlation between the OABSS and the IIEF-5. However, in HTLV-1 carriers, ED has been documented even in the absence of urinary dysfunction.[12]

The pathogenesis of ED in patients with definite and probable HAM/TSP is certainly related to spinal cord pathology and to neurologic lesions responsible for paraparesis and urinary manifestations.[19] However, the reasons why HTLV-1 carriers have ED are unclear, as well if ED could be an early neurologic manifestation. It is noteworthy that other neurologic symptoms and signs, such as paresthesia, low back pain, weakness, and hyperreflexia in the lower limbs, are more frequently documented in HTLV-1 carriers than in seronegative controls.[5] Moreover, in HTLV-1 infection, even in those who have definite HAM/TSP, the spinal cord pathology may be not documented by magnetic resonance imaging or other currently used methods.[19]

A cohort study aimed at describing the evolution of neurologic manifestations in HTLV-1 infection showed a slow progression of neurologic symptoms in 7 years of follow-up, and only a few patients with probable HAM/TSP evolved to definite HAM/TSP.[20] In our cohort, ED progressed slowly, but some men who were infected developed severe ED during follow-up. A Kaplan-Meyer survival analysis showed

that ED progression was faster in patients with definite HAM/TSP than in HTLV-1 carriers and probable HAM/TSP. However, in our cohort, there were men with mild or mild to moderate ED who did not have urologic or neurologic manifestations at baseline but who progressed to moderate and severe ED. Two patients who advanced to moderate ED developed overactive bladder late during follow-up. In addition, the 2 patients who developed definite HAM/TSP during follow-up developed severe ED before the onset of motor dysfunction. These data suggest that worsening ED may be a risk factor for the development of neurogenic bladder and definite HAM/TSP.

In a retrospective cohort study of patients with mild and moderate brain trauma, those who had a severe injury score $\geq$16 had a higher risk of developing more severe ED.[20] Neurologic disease caused by infectious agents may be associated with ED, and there is evidence that specific treatment of these infections can result in improvement of ED. For example, in patients with neuroschistosomiasis treated with praziquantel and pulse methylprednisolone therapy, followed by oral prednisone for 6 months, there was an improvement in magnetic resonance imaging findings and ED.[21] There is no specific therapy for HTLV-1 infection, but the use of drugs that relax the smooth muscle of the corpora cavernosa improves ED in individuals who are infected.[22]

An important limitation of cohort studies aimed at determining the evolution of clinical manifestations in individuals infected with HTLV-1 is the slow progression of neurologic manifestations. Therefore, even our follow-up of close to 10 years may not have been sufficient to observe significant disease progression. Our study was also limited by its modest sample size and for having incomplete data regarding the influence of traditional risk factors for ED, such as hypertension, diabetes mellitus, dyslipidemia, hormonal and psychogenic factors, and metabolic syndrome. Yet, we previously documented that neurologic disease is a more important risk factor for ED than metabolic, hormonal, or psychogenic abnormalities.[13,14] Other studies making a more specific neurologic evaluation, such as electroneuromyography, spinal magnetic resonance, and Doppler ultrasound of the penile arteries, may provide more information about ED in those infected with HTLV-1. However, this is the first prospective cohort study to assess ED in cases of HTLV-1 infection, and in addition to describing the evolution of ED in those with this viral infection, we observed in some patients that worsening of ED preceded the appearance of probable and definite HAM/TSP.

Conclusion

ED is a slow and progressive clinical manifestation of HTLV-1 infection, and progression to severe ED is faster in those with definite HAM/TSP. An inverse correlation between worsening of urinary dysfunction and the IIEF-5 was observed, and worsening of erectile function may precede the development of urinary dysfunction and motor disability in individuals infected with HTLV-1.

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