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Original Research

Vaginal dryness in women infected by human T-lymphotropic virus type 1: an exploratory study

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Abstract

Background: Human T-lymphotropic virus type-1 (HTLV-1) causes a variety of sicca symptoms, including xeroderma, xerostomia, and xerophthalmia.
Aim: We sought to evaluate vaginal dryness via the degree of perceived vaginal lubrication, vaginal hormonal cytology, and direct measurements of vaginal wetting.
Methods: The research was designed as a cross-sectional study. Vaginal dryness was assessed by scores in the lubrication domain of the Female Sexual Function Index (FSFI) questionnaire and the Vaginal Maturation Index (VMI) determined by vaginal hormonal cytology, as well as the measurement of vaginal lubrication using Schirmer strips placed at the anterior vaginal wall. Medians (25th-75th percentiles) were calculated for each group and compared using a nonparametric Kruskal-Wallis test and the Dunn-Bonferroni post hoc method.
Outcomes: Outcomes were detection of the presence of vaginal dryness in women who were infected or noninfected with HTLV-1.
Results: HTLV-1–infected women ($n = 72$, 57 asymptomatic and 15 with HTLV-1–associated myelopathy/tropical spastic paraparesis [HAM/TSP]) and uninfected women ($n = 49$) were studied. Women with HAM/TSP had significantly lower FSFI lubrication scores than asymptomatic and uninfected women ($P = .032$). In addition, women with HAM/TSP had significantly lower VMI compared with the asymptomatic and uninfected groups ($P = .027$ and $P = .039$, respectively).
Clinical Implications: The results of this study show a reduction in vaginal lubrication in HTLV-1-infected women diagnosed with HAM/TSP compared with asymptomatic and uninfected women.
Strengths and Limitations: The lack of a gold standard test for the diagnosis of vaginal dryness and the fact that no assessment of vaginal pH was performed were limitations of this study. The strength of the study was the comprehensive assessment of vaginal dryness from several perspectives: subjective (perception of vaginal lubrication according to the vaginal lubrication domain of the FSFI), hormonal (vaginal hormonal cytology to assess local hormone status), and the degree of vaginal moisture (direct measurement of vaginal dryness with an instrument, the Schirmer strip, already used to measure the presence of dry eye).
Conclusion: HTLV-1-infected women with HAM/TSP have decreased vaginal lubrication compared with asymptomatic and uninfected women after adjusting for age.

Keywords: HTLV-1; vaginal dryness; Female sexual function index; Vaginal maturation index.

Introduction

Human T-lymphotropic virus type-1 (HTLV-1) is transmitted through blood or contaminated tissue, from mother to child mainly through breastfeeding and via sexual intercourse.[1] This retrovirus is the etiologic agent of adult T-cell leukemia/-lymphoma (ATLL), HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP)[2,3] and uveitis.[4] An association between infection by HTLV-1 and Sjogren's syndrome has been suggested because HTLV-1–infected individuals present sicca symptoms such as xeroderma[5,6] and dry mouth, in addition to xerophthalmia, with increased frequency compared with uninfected individuals.[7-9] Signs of dryness involving the nose, trachea, and skin, in addition to vaginal dryness, are frequently found in patients with Sjogren's syndrome.[10]

Vaginal dryness is characterized by insufficient lubrication of the vaginal mucosa, which may cause burning, itching, dyspareunia and sexual dysfunction.[11,12] Recently, HAM/TSP was found to be associated with sexual dysfunction in women of reproductive age infected with HTLV-1. Accordingly, women with a diagnosis of HAM/TSP presented significant decreases in median scores of the lubrication domain on the Female Sexual Function Index (FSFI) questionnaire compared with asymptomatic and uninfected women.[13]

The diagnosis of vaginal dryness is based primarily on the patient's clinical complaints. This assessment is usually supported by other investigations, such as measurement of vaginal pH, determination of the vaginal maturation index (VMI), and/or measurement of follicle-stimulating hormone,

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luteinizing hormone, and serum estrogen.[14] To date, no specific test to evaluate vaginal lubrication has been standardized and validated. In the present study we aimed to confirm the association between the infection by HTLV-1 and vaginal dryness via the degree of perceived vaginal lubrication, vaginal hormonal cytology, and direct measurements of vaginal fluid.

Methods

Study design and location

The present study was designed as a cross-sectional study, and the outcome of interest was the presence of vaginal dryness in women infected and women not infected with HTLV-1. All women were consecutively selected from August 2014 to March 2016 during regular medical consultations at the Integrated and Multidisciplinary HTLV Center (CHTLV) in Salvador, Brazil. This outpatient clinic provides comprehensive biopsychosocial care to the public, supported by the National Unified Health Care System (SUS), including general medical treatment, laboratory diagnosis, psychological counseling, and physical therapy. Most infected patients were women (72.1%) aged 4-93 years and most (38.4%) had less than 8 years of formal education and earned less than the Brazilian minimum wage (US$ 215.00).[15]

Patients

The following inclusion criteria were considered: diagnosis of HTLV-1 infection (confirmed by enzyme-linked immunosorbent assay [ELISA] and Western blot), age between 20 and 50 years, and reported sexual activity in the 4 weeks before the time of the study. Consistent with neurologic examination, HTLV-1-infected women were classified as either clinically asymptomatic [no evidence of myeloneuropathy HTLV-1(+)], or as HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP).[16] The Expanded Disability Status Scale (EDSS)[17] and Osame's Motor Disability Score (OMDS)[18] were used to classify the absence of myelopathy when the OMDS was <1 and the EDSS score was ≤ 1.[19] The control group were selected from companions or relatives of patients who attended consultations and consisted of women who were not infected with HTLV-1 (ELISA negative). Women in the control group were paired with HTLV-1–infected women matched for age, presence of comorbidities, smoking, contraceptive methods, and presence of other sexually transmitted infections. Women with medical conditions (including a clinical diagnosis of depression) or who were undergoing treatments (eg, beta-blockers, antidepressants, CNS depressants, and anticholinergics) that might affect hormone production or sexual desire and women who had reached menopause were excluded.

Ethics

This study was approved by the IRB of the Bahiana School of Medicine and Public Health (EBMSP) (CAAE protocol number 33098414.4.0000.5544), and all women signed an informed consent form before participation.

Data collection

At the time of enrollment in the study, a questionnaire prepared by the authors was used to collect sociodemographic data and medical history (age, self-reported skin color, marital status, education level, income, number of previous births, number of lifetime sexual partners, age of current partner, and existing medical conditions, including systemic arterial hypertension, urinary incontinence, constipation, and diabetes mellitus). In addition, the Female Sexual Function Index (FSFI) was used to assess female sexual dysfunction, with 19 questions divided into 6 domains: sexual desire, sexual arousal, vaginal lubrication, orgasm, sexual satisfaction, and pain. Each domain has a different scoring system. The lubrication domain questions were scored from 0 to 6.[20] The vaginal lubrication domain consists of 4 questions about frequency of lubrication, difficulty in lubrication, and maintenance of lubrication until the end of sexual activity. After using the FSFI, each woman underwent a gynecologic examination. With the patient in a lithotomy position, after a thorough examination of the vulva and perineum, the vaginal walls and cervix were inspected with a speculum. The smear for evaluation of vaginal hormonal cytology was obtained from the upper third of the lateral wall of the vagina, a region particularly sensitive to hormonal stimuli. Finally, a Schirmer tear test strip (used as an additional test to diagnose dry eye)[21] was carefully placed by the anterior vaginal wall, superolaterally, in the proximal third, for 3 minutes. Vaginal lubrication was assessed using the following 3 clinical and laboratory parameters: (1) FSFI scores for vaginal lubrication; (2) VMI assessed by vaginal hormonal cytology to determine the cell maturation value (Meisels' index), which checks for changes in the proportion of vaginal epithelial cell types: parabasal, intermediate, and superficial[22]; and (3) an estimate of vaginal lubrication performed with Schirmer test strips.

Statistical analyses

The sample size was based on an estimated prevalence of 30% sexual dysfunction in uninfected women,[23] with an expected prevalence ratio of 2.0 between infected and uninfected individuals. With an alpha error of 5% and power of 80%, a minimum sample of 49 asymptomatic HTLV-infected women and an identical number of uninfected women (unexposed) were estimated. Among women with HAM/TSP (exposed), the estimated prevalence of sexual dysfunction was 80%.[24] Considering an unexposed/exposed ratio of 3:1, the resulting sample size of individuals with HAM/TSP was estimated to be at least 12.[13]

Descriptive statistics were used to characterize FSFI domain vaginal lubrication, VMI, and Schirmer test strip wetting results expressed in millimeters. Comparisons of vaginal lubrication parameters between HTLV-1–infected (HAM/TSP, asymptomatic) and uninfected women were performed using the nonparametric Kruskal-Wallis test with Bonferroni-Dunn post hoc analysis. The Fischer exact test was used to compare dichotomous descriptors of vaginal lubrication between infected (asymptomatic and HAM/TSP) and uninfected groups. Spearman's correlation analysis was used to assess correlations between FSFI scores for vaginal lubrication, VMI, Schirmer test strip wetting, and age.

Vaginal dryness was assessed using the following indicators: FSFI domain scores for vaginal lubrication below the 10th percentile of the uninfected group (score = 2.7), VMI $\leq 50\%$,[25] and ≤ 5 mm wetting on Schirmer strips.[21] Multiple linear regression was performed to evaluate the effect of age on indicators of vaginal lubrication. P values $<.10$ and $<.05$ were

Table 1. Sociodemographic and clinical characteristics of 121 women evaluated at CHTLV in Salvador, Bahia-Brazil.

Variable	Uninfected	HTLV-1–infected women		*P*
		HTLV(+)	HAM/TSP	
Age, mean (SD) years	35.6 (7.9)	34.2 (7.2)	41.1 (6.1)	.007
Skin color, *n* (%)				.064[a]
Black	25 (51.0)	30 (52.6)	05 (33.3)	
Brown	22 (45.8)	18 (31.6)	08 (53.3)	
White	02 (4.1)	09 (15.8)	01 (6.7)	
Yellow	—	—	01 (6.7)	
Educational level, median (IQR) years	12.0 (8.0-12.0)	09 (5.0-12.0)	12 (8.0-14.0)	.064[b]
Marital status, *n* (%)				.095
Married/stable union	35 (71.4)	44 (77.2)	8 (53.3)	
Single	11 (22.5)	13 (22.8)	7 (46.7)	
Divorced/separated	03 (6.1)	—	—	
Self-reported income, MW	2.0 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	.021[b]
Partner age, mean (SD) years	38.3 (9.8)	39.4 (9.5)	46.7 (4.9)	.033[b]
No. of partners, median (IQR)	4.0 (2.0-7.0)	5.0 (3.0-12.0)	4.0 (3.0-7.0)	.401[b]
No. of previous births, median (IQR)	2.0 (1.0-2.0)	1.0 (1.0-3.0)	2.0 (0.0-3.0)	.803[b]
Systemic Arterial Hypertension (SAH), *n* (%)				.365[a]
Present	04 (8.2)	10 (17.5)	01 (7.1)	
Absent	45 (91.8)	47 (82.5)	13 (92.9)	
Urinary incontinence, *n* (%)				<.001[a]
Present	03 (6.1)	12 (21.0)	10 (71.4)	
Absent	46 (93.9)	45 (79.0)	04 (28.6)	
Constipation, *n* (%)				<.001[a]
Present	01 (2.0)	11(19.3)	08 (57.1)	
Absent	48 (98.0)	46 (80.7)	06 (42.9)	
Diabetes mellitus, *n* (%)				>.999[a]
Present	03 (6.1)	03(5.3)	—	
Absent	46 (93.9)	54 (94.7)	14 (100.0)	

CHTLV, Integrated and Multidisciplinary HTLV Center; HAM/TSP, human T-lymphotropic virus type-1–associated myelopathy/tropical spastic paraparesis; HTLV, human T-lymphotropic virus; HTLV-1, HTLV type-1; MW, minimum wage (approximately US$ 300 as of October 2017). [a] Fisher's exact test. [b] Kruskal-Wallis test.

considered statistically borderline and significant, respectively. All analyzes were performed using STATA for MacOS, version 13.0, or Prism for MacOS, version 9.3.1.

Results

A total of 121 women [15 with a definite diagnosis of HAM/TSP, 57 HTLV-1(+), and 49 uninfected] were included. The mean (SD) age of the HAM/TSP group was higher than that of the HTLV-1(+) group (41.1 [6.1] vs 34.2 [7.2] years; $P < .001$), as was the case for uninfected women (35.6 [7.9]; $P = .007$]). No differences were found between groups in self-reported skin color ($P = .064$), education level ($P = .064$), and marital status ($P = .095$). Income ($P = .021$) was lower for the HTLV-1(+) group (Table 1). The women with HAM/TSP had neurological impairments ranging from discrete lower-limb strength loss (EDSS = 2), which was found in 8 patients, to the need for a wheelchair (EDSS = 7), which occurred in one 45-year-old woman.

Median scores (25th-75th percentile) for the vaginal lubrication domain of the FSFI were similar between the HTLV-1(+) (4.8 [3.9-5.4]) and uninfected groups (4.8 [4.2-5.7]), while women with HAM/TSP had lower scores (4.2 [2.7-5.1]; $P = .032$). The VMI scores and vaginal fluid measurements performed with Schirmer test strips were significantly higher in HTLV-1(+) women and the uninfected control group than in the HAM/TSP group (Figure 1), whereas they were similar in HTLV-1(+) women and the uninfected control group. No significant differences were observed in the proportion of women with respect to FSFI lubrication domain scores below the 10th percentile (<2.7). However, wetting ≤5 mm on Schirmer test strips and VMI ≤50% were diagnosed more frequently in women with HAM/TSP than those with HTLV-1(+) and uninfected individuals ($P = .034$ and $P = .003$, respectively) (Table 2).

Correlation analysis revealed a significant positive correlation between vaginal wetting with Schirmer test strips (measured in mm) and VMI ($r = 0.2234$; $P = .014$) and a negative correlation with age ($r = -0.3075$; $P < .01$) (Table 3). HTLV-1 infection status (from uninfected to diagnosis HAM/TSP) was inversely correlated with FSFI lubrication domain scores ($r = -0.2079$; $P < .05$) and VMI ($r = -0.1902$; $P < .01$), (Table 3). The degree of neurological dysfunction, as measured by the EDSS, did not correlate with any of the vaginal lubrication parameters studied (data not shown).

We then used linear regression analysis to examine the effect of age on FSFI scores for vaginal lubrication, VMI, and vaginal wetting measured by Schirmer test strips, using uninfected individuals as a reference to assess the HTLV-1(+) and HAM/TSP groups (Table 4). Women with HAM/TSP had significantly lower FSFI scores for lubrication ($\beta = -1.067$; 95% CI, −1.822 to −0.311) compared with uninfected subjects, suggesting an average reduction in this FSFI score of approximately one point. HAM/TSP was also independently associated with VMI ($\beta = -9.061$; 95% CI, −16.766 to −1.354), indicating an average reduction in the index of 9.0% in women with myelopathy (Table 4). With respect to the use of the Schirmer test strip, HAM/TSP appeared to have a borderline effect on reducing vaginal wetting ($P = .061$). However, age showed a negative correlation with vaginal wetting on

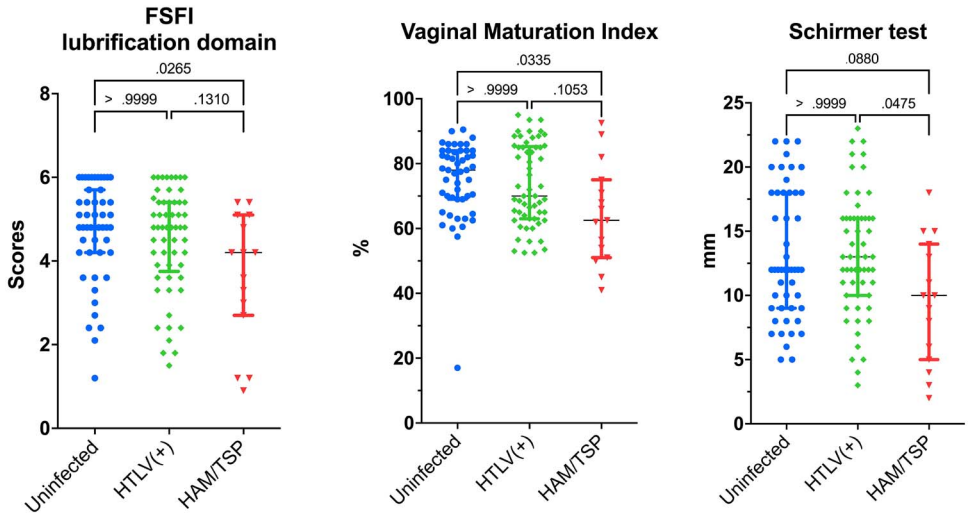

Figure 1. Comparison of the values of the domain scores of the vaginal lubrication of the FSFI, vaginal maturation index and vaginal wetting assessed by Schirmer test strip between women uninfected, HTLV-1(+) asymptomatic and with HAM/TSP. FSFI, Female Sexual Function Index; HAM/TSP, human T-lymphotropic virus type-1–associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-lymphotropic virus type-1.

Table 2. Distribution of values of scores of vaginal lubrication by the FSFI, VMI, and vaginal dryness (Schirmer test), according to the condition of infection (HAM/TSP, HTLV-1, and uninfected).

Vaginal lubrication parameter	Group[a]			*P*
	HAM/TSP (*n* = 15)	HTLV-1(+) (*n* = 57)	Uninfected (*n* = 49)	
LD (FSFI)	4.2 (2.7-5.1)	4.8 (3.9-5.4)	4.8 (4.2-5.7)	.032[b]
VMI (%)	62.5 (51.0-75.0)	70.0 (63.0-85.0)	78.0 (69.0-84.0)	.039[b]
Schirmer test, mm[d]	10.0 (5.0-14.0)	13.0 (10.0-16.0)	12.0 (9.0-18.0)	.049[b]
LD (FSFI) < 2.7	4 (26.7)	8 (14.0)	5 (10.2)	.330[c]
VMI ≤ 50%	3 (20.0)	—	1 (2.0)	.003[c]
Schirmer test ≤5 mm[d]	4 (26.7)	4 (7.0)	2 (4.1)	.034[c]

FSFI, Female Sexual Function Index; HAM/TSP, human T-lymphotropic virus type-1–associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-lymphotropic virus type-1; LD, lubrication domain on FSFI; VMI, vaginal maturation index. [a]Values are presented as median (25th-75th percentile) or *n* (%) of patients. [b]$P < .05$, Kruskal-Wallis test. [c]$P < .05$, Fisher's exact test. [d]Vaginal wetting assessed by Schirmer test strip (mm).

Table 3. Correlation coefficients (*r*) between the scores of the domain of vaginal lubrication FSFI, VMI, vaginal dryness (Schirmer test), age, and condition in relation to infection among the 121 women studied.

Variables	Correlation coefficient, *r*				
	Age	Lubrication	VMI	Schirmer strip (mm)	Group[a]
Age	1.0	—	—	—	—
LD (lubrication)	−0.1054	1.0	—	—	—
VMI	−0.1251	0.1731	1.0	—	—
Schirmer strip (mm)[a]	−0.3075**	0.0791	0.2234*	1.0	—
HTLV-1 status[a]	0.0897	−0.2079*	−0.1902*	−0.1191	1.0

FSFI, Female Sexual Function Index; HAM/TSP, human T-lymphotropic virus type-1–associated myelopathy/tropical spastic paraparesis; HTLV-1, HTLV type-1; LD, lubrication domain on FSFI; VMI, vaginal maturation index. [a]Schirmer strip (mm) and HTLV-1 status, $^{**}P < .01$; $^{*}P < .05$. HTLV-1 infection status was scored as follows: 0, HTLV negative; 1, HTLV-1 positive asymptomatic; 2, HAM/TSP.

the test strip regardless of infection status, with an average reduction of 0.17 mm for each additional year ($\beta = -0.169$; 95% CI, −0.286 to −0.052).

Discussion

In the present study, it was found that women diagnosed with HAM/TSP had increased vaginal dryness compared with asymptomatic HTLV-1-infected women and uninfected controls. Both FSFI scores for vaginal lubrication and VMI were significantly lower in women with HAM/TSP, even after adjusting for the effect of age on vaginal lubrication. Although the women with HAM/TSP were older than the asymptomatic and uninfected women, none of them were in menopause, which could influence lubrication due to hormonal factors. In the HAM/TSP group, an average decrease of 1 point on the FSFI Vaginal Lubrication domain score was observed, representing a decrease of almost 20% (domain scale range 0-6 points).[20] In addition, when age was taken into account the VMI in women with HAM/TSP was 9% lower than the VMI in uninfected controls. The association between HAM/TSP and vaginal dryness was also supported by the finding that 10 times more women with HAM/TSP had VMI below 50% than women not infected with HTLV-1.

Table 4. Effects of HAM/TSP, HTLV-1 infection, and age on the range of FSFI vaginal lubrication scores (model 1), VMI (model 2), and vaginal lubrication assessed with Schirmer test strips (model 3) in the 121 women studied.

Variables	β	95 CI%	*P*
Model 1 (FSFI lubrication domain)			
Uninfected (reference)			
Asymptomatic	−0.233	−0.721 to 0.255	.346
HAM/TSP	−1.067	−1.822 to −0.311	.006
Age (years)	−0.006	−0.037 to 0.025	.694
Model 2 (VMI)			
Uninfected (reference)			
Asymptomatic	−1.665	−6.643 to 3.312	.509
HAM/TSP	−9.061	−16.766 to −1.354	.022
Age (years)	−0.251	−0.569 to 0.067	.121
Model 3 (Schirmer's test strip in mm)			
Uninfected (reference)			
Asymptomatic	−0.196	−2.026 to 1.633	.832
HAM/TSP	−2.706	−5.538 to 0.126	.061
Age (years)	−0.169	−0.286 to −0.052	.005

FSFI, Female Sexual Function Index; HAM/TSP, human T-lymphotropic virus type-1–associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-lymphotropic virus type-1; VMI, vaginal maturation index.

Vaginal lubrication occurs during the first phase of female sexual response. Vaginal fluid is produced by plasma transudation through the vaginal epithelium into the vagina, in addition to mucus produced by the uterine, vestibular, and Bartholin glands. These responses depend on the autonomic innervation of the female genitalia and are controlled by the sympathetic and parasympathetic nervous systems.[26]

Several factors influence vaginal lubrication, such as decreased estrogen and/or testosterone levels and/or the use of medications that impair sexual desire (beta-blockers, antidepressants, CNS depressants, and anticholinergics).[14] Infection with HTLV-1 has been associated with various sicca symptoms, such as dry eye,[7,9] xerostomia,[8,27] and xeroderma.[5,28] Sjogren's syndrome has been described in individuals infected with HTLV-1.[7,29,30] In particular, a high prevalence of Sjogren's syndrome has been noted in individuals diagnosed with HAM/TSP.[31,32] Inflammation of the salivary glands has been described in patients with dry eye.[33] HTLV-1 infection induces proinflammatory cytokines in the cervicovaginal fluid of asymptomatic women, even in the presence of a low vaginal HTLV-1 proviral load.[34] This inflammatory response may damage the vaginal fluid–secreting glands, as has been observed in lacrimal and salivary glands.[30] However, this hypothesis has not been investigated. On the other hand, the dryness of the vaginal mucosa in women with HAM/TSP may be attributable to changes in the autonomic nervous system. The vagina receives sympathetic efferent fibers from the lower thoracic segments and parasympathetic fibers from the sacral segments. Myelopathic involvement caused by HTLV affecting parasympathetic fibers may result in increased vaginal dryness. Indeed, one of the possible changes caused by HTLV-1, especially in patients with HAM/TSP, is demyelination of the pyramidal tract with axonal loss, mainly in the lower thoracic spinal cord, affecting the response to stimuli from this filament reflex arc.[35]

The lack of a gold standard test for the diagnosis of vaginal dryness and the fact that a vaginal pH assessment was not performed were limitations of this study. The strength of the study was the broad evaluation of vaginal dryness from different perspectives: subjective (patient perception of vaginal lubrication by the vaginal lubrication domain of the FSFI), hormonal (vaginal hormonal cytology to check local hormonal status), and vaginal moisture (direct measurement of vaginal dryness with an instrument, the Schirmer strip, already used to measure the presence of dry eye).[21] Because there is no minimum vaginal lubrication score (FSFI) to determine specific disorders, we used the 10th percentile score of the group of uninfected women as a cutoff for the presence of vaginal dryness. Although there was no statistically significant difference in the range of vaginal lubrication, the proportion of women with a score of less than 2.7 in the HAM/TSP group was 2.5 times higher than the proportion in the asymptomatic and uninfected group. Other quantitative parameters used to measure vaginal dryness, such as the Schirmer strip and VMI, were significantly associated with lower vaginal lubrication in women with HAM/TSP, supporting the biological plausibility of vaginal dryness in women with HAM/TSP.

In summary, the results of this study show that compared with asymptomatic and uninfected women, HTLV-1–infected women diagnosed with HAM/TSP have a reduction in vaginal lubrication. These women need gynecologic and psychological monitoring to assess changes in vaginal lubrication and gynecologic counseling and guidance to have a satisfactory sex life.

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Conflict of interest: We declare that we have no conflict of interest.

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