# Urinary Symptoms Associated with Human T-Cell Lymphotropic Virus Type I Infection: Evidence of Urinary Manifestations in Large Group of HTLV-I Carriers

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**OBJECTIVES** To describe the frequency of urologic manifestations in human T-cell lymphotropic virus type I (HTLV-I) seropositive individuals from Salvador and other cities in Bahia, Brazil, with or without clinical HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP).

**METHODS** A total of 218 HTLV-I seropositive subjects referred from blood banks or neurologic clinics were admitted to the HTLV-I multidisciplinary outpatient clinic from January 2001 to April 2004. They were assessed using a standardized questionnaire to determine urinary complaints and quality of life. Neurologic impairment was established using the Expanded Disability Status Scale (EDSS). HAM/TSP was considered as an EDSS score of 2 or greater.

**RESULTS** Nocturia (35.8%) was the most frequent finding, followed by incontinence (29.8%), urgency (25.2%), frequency (22.0%), and dysuria (15.6%). Differences were found between individuals with an EDSS score of 0 and those with an EDSS score greater than 0 but less than 2 regarding frequency, nocturia, urgency, urinary loss of any degree, and quality of life. Dysuria and great or total urinary loss were more frequent among those with severe HAM/TSP (EDSS score greater than 6).

**CONCLUSIONS** Even HTLV-I subjects considered not to have HAM/TSP may have prominent urinary findings already present. Urologic manifestations, including nocturia and urinary loss, might be early manifestations of neurologic disease in those with HTLV-I. UROLOGY 69: 813–818, 2007. © 2007 Elsevier Inc.

Human T-cell lymphotropic virus type I (HTLV-I) is a retrovirus that has been demonstrated to be the etiologic agent in adult T-cell leukemia and a progressive neurologic disorder called HTLV-I-associated myelopathy (HAM) or tropical spastic paraparesis (TSP).[1] Differently from human immunodeficiency virus infection, HTLV-I infection is not related to acquired immunodeficiency syndrome. HAM/TSP is characterized by spastic paraparesis with generalized increased deep tendon reflexes, bilateral Babinski's sign, deep sensation abnormalities, and severe bladder dysfunction.[2] The prevalence of HTLV-I infection is approximately 20 million worldwide, with endemic foci in the Caribbean, South America, Western Africa, and Japan.[3] It is estimated that in the United States approximately 266,000 individuals are infected with HTLV-I or HTLV-II. Of these, it is likely that more than 3600 people in the United States have unrecognized HAM/TSP.[4] The vast majority of HTLV-I-infected individuals are clinically asymptomatic, and less than 5% of seropositive subjects develop HAM/TSP.[5]

Urologic manifestations are present in up to 90% of patients with HAM/TSP and are characterized by frequency, urgency, and urge incontinence.[6–8] However, most of the available data are limited to case reports and descriptions of the overall clinical picture in patients with overt disease, with neither emphasizing the urologic aspects nor classifying the individuals according to their clinical or neurologic impairment.[7–15]

The purpose of this study was to describe the frequency of urologic manifestations in HTLV-I-infected individuals from a multidisciplinary HTLV-I outpatient department and to verify whether these manifestations correlated with age, sex, and overall neurologic impairment.

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**Table 1.** Mean age, sex, and classification of HTLV-I seropositive individuals according to EDSS score

| Classification | EDSS | n (%) | Male/Female (*P* Value*) | Mean Age (yr) (SD) | Group |
|---|---|---|---|---|---|
| HTLV-I carriers | 0 | 119 (54.6) | 65/54 (NA) | 40.9 (12.5) | 1A |
| | 1.0–1.5 | 55 (25.3) | 29/26 (NA) | 41.7 (12.3) | 1B |
| Subtotal | 0–1.5 | 174 (79.8) | 94/80 (0.82) | 41.1 (12.4) | 1 |
| Mild to moderate HAM/TSP | 2.0–6.0 | 33 (15.2) | 14/19 (NA) | 51.3 (13.0) | 2A |
| Severe HAM/TSP | 6.5–8.0 | 11 (5.0) | 3/8 (NA) | 54.9 (11.3) | 2B |
| Subtotal | 2.0–8.0 | 44 (21.2) | 17/27 (0.59)† | 52.2 (12.6) | 2 |
| Total | 0–8.0 | 218 (100) | 111/107 (0.07) | 43.4 (13.2) | NA |

HTLV-I = human T-cell lymphotropic virus type I; EDSS = Expanded Disability Status Scale; HAM/TSP = HTLV-I-associated myelopathy/tropical spastic paraparesis.
* Pearson chi-square test.
† Continuity correction.

## MATERIAL AND METHODS

From January 2001 to April 2004, 218 HTLV-I seropositive individuals (111 men and 107 women) were evaluated at the Hospital Universitário Professor Edgard Santos/Universidade Federal da Bahia multidisciplinary HTLV-I outpatient department in Salvador, Brazil. The HTLV-I-positive individuals were referred from blood banks or other neurologic services throughout the state. In all cases, the diagnosis of HTLV-I infection was established by enzyme-linked immunosorbent assay and confirmed by Western blot analysis. The HTLV-I-positive individuals were then evaluated by several specialists in an ordered and consecutive fashion. They underwent complete clinical, neurologic, and urologic evaluations.

Neurologic disability was established using the Expanded Disability Status Scale (EDSS).[16] This scale is a good predictor of neurologic impairment in patients with multiple sclerosis, because it evaluates the compromise of multiple functional systems, including pyramidal, sensory, bladder, bowel, visual, cerebellar, and mental functions. Because of the similarities in the pathogenesis and clinical picture of multiple sclerosis and HAM/TSP, this scale has been widely used to evaluate the disease severity in patients with HAM/TSP.[17] The scale ranges from 0 (normal) to 10 (death from HAM/TSP). Because there is no validated scale able to provide such a comprehensive assessment of HTLV-I-infected individuals and simply describing the neurologic findings would add subjectivity and lack of reproducibility, the EDSS seemed to be the most suitable option. HTLV-I-associated myelopathy was clinically defined as an EDSS score of 2 or more. Patients were initially divided into two groups: HTLV-I carriers (group 1), composed of individuals who did not fulfill the criteria for HTLV-I-associated myelopathy (EDSS score less than 2); and patients with HAM/TSP (group 2) who had an EDSS score of 2 or more. Also, the individuals in the first and second groups were divided into subgroups according to the EDSS score to differentiate in relation to disease severity. A total of 44 individuals (17 men and 27 women) had clinically defined HAM/TSP (group 2).

These subjects were also assessed by the assisting urologist (N.C.) using a semistructured anamnesis with physical examination and laboratory evaluation. The standardized questionnaire, the Urogenital Distress Inventory, to determine the occurrence of urinary complaints[18] and a quality-of-life (QOL) questionnaire (DITROVIE)[19] were also used. The Urogenital Distress Inventory is a validated questionnaire used to assess the occurrence of urinary complaints, as well as the degree to which these symptoms are troubling. The duration of illness was considered from the date of diagnosis of HTLV-I infection. Frequency was defined as more than eight micturitions daily and nocturia as getting up two or more times to urinate during the night. Urgency was considered to be a sudden desire to void, and dysuria as painful urination or vesical discomfort. Patients who presented with any of these urinary complaints were referred for urodynamic evaluation to obtain additional information about the bladder dysfunction. Individuals presenting with urinary symptoms also underwent urinalysis and urine culture. Those with urinary tract infection were treated before enrollment in this study.

The enrollment criteria were as follows: age 18 years or older and HTLV-I positive serology (enzyme-linked immunosorbent assay and Western blot). The collected data were inserted in a data bank and analyzed with the help of two statistical packages (Statistical Package for Social Sciences, version 11.5, and GraphPad Prism, version 3.0). Statistical significance was considered if $P < 0.05$.

The Ethical Committee of the Hospital Universitário Prof. Edgard Santos/Universidade Federal da Bahia approved this study.

## RESULTS

Of the 218 HTLV-I seropositive individuals, 50.9% were men. The age range was 18 to 81 years (mean 43.4 ± 13.2). The frequency of the urinary complaints in the overall HTLV-I seropositive population (HTLV-I carriers and patients with HAM/TSP), in descendent order, was as follows: nocturia (35.8%), urinary loss (29.8%), urgency (25.2%), frequency (22%), and dysuria (15.6%). Also, 26% of the subjects reported having a "bad" or a "very bad" QOL related to the urinary symptoms.

The subjects' classification according to the EDSS, group division, sex, and mean ± SD age is given in Table 1. No statistically significant difference was found in the sex distribution within the groups. In contrast, urinary manifestations were more prominent in women (urinary loss, frequency, nocturia, urgency). They also presented with a more severely compromised QOL (Table 2). Individuals in group 1 were younger than the patients in group 2 (Mann-Whitney *U* test, $P < 0.0001$). However, no differences were found in age among the subgroups within the same group. The median EDSS score in group 1 was 0.0 and in group 2 was 4.0. The median EDSS score in subgroup 2A was 3.0 and in subgroup 2B was 7.5.

**Table 2.** Frequency of urologic manifestations and quality-of-life compromise in HTLV-I seropositive individuals according to sex

| Variable | Male n (%) | Female n (%) | Odds Ratio (95% CI) | *P* Value* |
|---|---|---|---|---|
| Nocturia | | | | |
| 0 = No | 81 (73) | 58 (54.7) | 2.2 (1.3–3.9) | 0.005† |
| 1 = Yes | 30 (27) | 48 (45.3) | | |
| Urinary loss | | | | |
| 0 = No | 94 (85.5) | 58 (56.3) | 4.5 (2.4–8.8) | <0.0001† |
| 1 = Yes | 16 (14.5) | 45 (43.7) | | |
| Urgency | | | | |
| 0 = No | 95 (85.6) | 67 (63.3) | 3.5 (1.8–6.7) | 0.0001† |
| 1 = Yes | 16 (14.4) | 39 (36.8) | | |
| Frequency | | | | |
| 0 = No | 97 (87.4) | 72 (67.9) | 3.3 (1.6–6.5) | 0.001† |
| 1 = Yes | 14 (12.6) | 34 (32.1) | | |
| Urinary loss degree | | | | |
| 0 = Minor or moderate | 14 (82.4) | 34 (70.8) | — | 0.5‡ |
| 1 = Great or total | 3 (17.6) | 14 (29.2) | | |
| Dysuria | | | | |
| 0 = No | 94 (84.7) | 89 (84) | — | 0.88 |
| 1 = Yes | 17 (15.3) | 17 (16) | | |
| Quality of life | | | | |
| 0 = Normal or comfortable | 92 (82.9) | 65 (62.5) | 2.9 (1.5–5.5) | 0.001† |
| 1 = Bad or very bad | 19 (17.1) | 39 (37.5) | | |

HTLV-I = human T-cell lymphotropic virus type I; CI = confidence interval.
* Pearson chi-square test.
† Statistically significant.
‡ Continuity correction.

**Table 3.** Frequency of urologic manifestations and quality-of-life compromise in HTLV-I carriers and HAM/TSP patients

| Variable | HTLV-I Carriers n (%) | HAM/TSP Patients n (%) | Odds Ratio (95% CI) | *P* Value* |
|---|---|---|---|---|
| Nocturia | | | | |
| 0 = No | 131 (75.3) | 8 (18.6) | 13.3 (5.7–30.9) | <0.0001 |
| 1 = Yes | 43 (24.7) | 35 (81.4) | | |
| Urinary loss | | | | |
| 0 = No | 143 (82.2) | 9 (23.1) | 15.4 (6.6–35.6) | <0.0001 |
| 1 = Yes | 31 (17.8) | 30 (76.9) | | |
| Urgency | | | | |
| 0 = No | 151 (86.8) | 11 (25.6) | 19.1 (8.5–43.1) | <0.0001 |
| 1 = Yes | 23 (13.2) | 32 (74.4) | | |
| Frequency | | | | |
| 0 = No | 152 (87.4) | 17 (39.5) | 10.6 (4.9–22.5) | <0.0001 |
| 1 = Yes | 22 (12.6) | 26 (60.5) | | |
| Urinary loss degree | | | | |
| 0 = Minor or moderate | 28 (90.3) | 20 (58.8) | 6.5 (1.6–25.8) | 0.004 |
| 1 = Great or total | 3 (9.7) | 14 (41.2) | | |
| Dysuria | | | | |
| 0 = No | 157 (90.2) | 26 (60.5) | 6.0 (2.7–13.3) | <0.0001 |
| 1 = Yes | 17 (9.8) | 17 (39.5) | | |
| Quality of life | | | | |
| 0 = Normal or comfortable | 149 (86.1) | 8 (19.0) | 26.4 (10.9–63.8) | <0.0001 |
| 1 = Bad or very bad | 24 (13.9) | 34 (81.0) | | |

CI = confidence interval; other abbreviations as in Table 1.
* Pearson chi-square test; all *P* values statistically significant.

The frequency of urinary symptoms in HTLV-I carriers and patients with HAM/TSP is shown in Table 3. The occurrence of all complaints related to lower urinary tract involvement was greater in patients with HAM/TSP than in HTLV-I carriers. Nocturia, urinary loss, and urgency were the most frequent complaints, and at least one of these manifestations was present in up to 84.1% of patients with HAM/TSP. However, complaints related to urinary symptoms were also observed in a large population of individuals considered as HTLV-I carriers. Urodynamic studies were performed in a subset of 35 HTLV-I carriers, and detrusor overactivity was the

**Table 4.** Frequency of urologic manifestations and quality of life compromise in HTLV-I carriers according to EDSS classification

| Variable | Group 1A (EDSS = 0) n (%) | Group 1B (EDSS >0 to <2) n (%) | Odds Ratio (95% CI) | *P* Value* |
|---|---|---|---|---|
| Nocturia | | | | |
| 0 = No | 98 (82.4) | 33 (60.0) | 3.1 (1.5–6.4) | 0.001† |
| 1 = Yes | 21 (17.6) | 22 (40.0) | | |
| Urinary loss | | | | |
| 0 = No | 103 (86.6) | 40 (72.7) | 2.4 (1.1–5.3) | 0.027† |
| 1 = Yes | 16 (13.4) | 15 (27.3) | | |
| Urgency | | | | |
| 0 = No | 109 (91.6) | 42 (76.4) | 3.4 (1.4–8.3) | 0.006† |
| 1 = Yes | 10 (8.4) | 13 (23.6) | | |
| Frequency | | | | |
| 0 = No | 110 (92.4) | 42 (76.4) | 3.8 (1.5–9.5) | 0.003† |
| 1 = Yes | 9 (7.6) | 13 (23.6) | | |
| Urinary loss degree | | | | |
| 0 = Minor or moderate | 15 (93.8) | 13 (86.7) | — | 0.6‡ |
| 1 = Great or total | 1 (6.3) | 2 (13.3) | | |
| Dysuria | | | | |
| 0 = No | 110 (92.4) | 47 (85.5) | — | 0.149 |
| 1 = Yes | 9 (7.6) | 8 (14.5) | | |
| Quality of life | | | | |
| 0 = Normal or comfortable | 108 (91.5) | 41 (74.5) | 3.7 (1.5–9.0) | 0.003† |
| 1 = Bad or very bad | 10 (8.5) | 14 (25.5) | | |

Abbreviations as in Table 1.
* Pearson chi-square test.
† Statistically significant.
‡ Fisher's exact test.

most frequent abnormality, found in 42.4% of those cases.

No statistically significant difference between subgroups 1A and 1B in relation to dysuria and urinary loss degree was found. However, differences were found between these two subgroups in regard to the occurrence of frequency, nocturia, urgency, urinary loss of any degree, and QOL (Table 4). Within group 2, statistically significant differences were found between subgroups 2A and 2B concerning the occurrence of dysuria (28.1% versus 72.7%, respectively; $P = 0.009$, odds ratio 6.82, 95% confidence interval 1.47 to 31.61) and degree of urinary loss (78.3% versus 18.2% for minor or moderate urinary loss and 21.7% versus 81.8% for great or total loss, respectively; $P = 0.001$, odds ratio 16.20, 95% confidence interval 2.61 to 100.45).

The duration from the HTLV-I infection diagnosis was longer in group 2 than in group 1 (35.1 months versus 25.6 months, respectively; Mann-Whitney *U* test, $P = 0.02$), but no significance was seen when the subgroups within each group were compared.

## COMMENT

Urinary symptoms are common complaints in patients with HAM/TSP. We have provided evidence that a large proportion of individuals who do not fulfill the criteria for HAM/TSP have urinary symptoms and urodynamic abnormalities similar to those identified in the patients with HAM/TSP, indicating that urinary manifestations may be an early manifestation of HAM/TSP. The reported differences among the individuals within group 1 (EDSS score less than 2) have demonstrated that urinary symptoms can be a part of the initial clinical picture of central nervous system (especially of the spinal cord) involvement in HTLV-I infection. These complaints may also present as urodynamic translation,[20] in particular, the occurrence of irritative lower urinary tract symptoms. Among these symptoms, nocturia was the most frequent finding, despite the limited number of published studies that have described nocturia as part of the urinary manifestations in HTLV-I infection.[21]

Urinary loss was the second most frequent complaint. The individuals in group 2 (EDSS score of 2 or more) had a 15.4-fold greater risk of presenting with this symptom than the individuals in group 1. Moreover, within group 2, patients with severe HAM/TSP (EDSS score greater than 6) were also at a greater risk of developing great or total incontinence than were the patients with a milder condition (EDSS score of 2 or more but not more than 6; odds ratio 16.20). It is expected that the greater the overall compromise, the more severe the urinary manifestations. The available data reporting incontinence as a prominent urologic feature in HTLV-I infection have been based, almost exclusively, on case reports.[7,11,22–24]

Frequency was a less common symptom than nocturia or urinary loss. This might have been because individuals who wake up three or more times during the night or have any degree of incontinence may recall symptoms more readily than those who experience a slight increase

in the number of urinations during the day. Although frequency is usually one of the most referred urinary complaints described in published reports,[11,12,15] our data have indicated that nocturia and urinary loss are the most frequent urinary symptoms in those infected with HTLV-I. The same explanation may also apply to urgency, because patients might not realize that a sudden desire to void represents a problem, as long as they can urinate in a timely fashion.

Dysuria has also been described as an important manifestation and is thought to be due to detrusor and external sphincter dyssynergia, with detrusor hypocontractility also considered as a possible cause.[14] The prevalence of dysuria was significantly greater statistically in group 2 than in group 1. Within group 2, patients with severe HAM/TSP (subgroup 2B) also presented with a greater frequency of this complaint than did the patients with mild to moderate HAM/TSP (subgroup 2A).

The individuals stratified to group 1 were younger than those in group 2, but no differences were seen between the subgroups within each group. The subgroup comparisons, however, might have had limited power owing to the smaller sample sizes within each group. The age difference between groups could reflect the chronic and progressive nature of the disease, because the individuals in group 1 also had had a shorter duration of HTLV-I infection and, hence, possibly less exposure to this virus and less opportunity to develop clinical disease.

The greater frequency of great or total urinary loss and dysuria in the HAM/TSP group compared with the HTLV-I carrier group was expected owing to a compromise of the lateral corticospinal tract. Such degeneration, in a more advanced stage, is capable of producing neurogenic bladder obstructive features rather than only irritative symptoms, as seen in the earlier stages of the disease. Dysuria and greater degrees of urinary loss were also more frequent among the patients with severe HAM/TSP than among those with a milder condition, giving additional support to the observation that obstructive symptoms are more frequent because of a more seriously and chronically damaged spinal cord.

We observed an unusually high percentage of men in the studied population, which could have been because of the overall greater proportion of male blood donors, once the majority of the individuals were screened by blood donation. We also found a slight predominance of HTLV-I infection among male subjects; however, HAM/TSP was more frequent among women, in accordance with the findings of previous studies.[25]

Most reports have presented spinal cord atrophy as the main radiologic finding in patients with HAM/TSP. The most vulnerable site is the lower thoracic spinal cord, and infiltration of mononuclear leukocytes has been observed in the spinal cord.[26] Spinal cord magnetic resonance imaging is not included in the World Health Organization criteria. It would be important to exclude other causes of gait disturbance in HTLV-I-positive subjects; however, it would make this study economically unviable.

In regions with a low prevalence of HTLV infection, subjects with persistent lower urinary tract symptoms of "idiopathic" etiology and abnormal urodynamic findings should undergo HTLV serology testing, especially if these individuals present with other neurologic symptoms. In regions of high prevalence, this hypothesis should be raised during the initial diagnostic workup. Ideally, these patients should be assisted by a multidisciplinary group composed of urology, neurology, hematology, and infectious disease specialists.

## CONCLUSIONS

We observed that a high percentage of individuals genuinely considered as HTLV-I carriers have urinary symptoms. These manifestations could not be explained by sex, urinary tract infection, or the occurrence of other neurologic diseases. The fact that the most common urinary complaints in patients with HAM/TSP (nocturia, incontinence, and urgency) were also the most common manifestations observed in HTLV-I carriers with an EDSS score of 0.0 to 2.0 supports the argument that these manifestations are related to HTLV-I infection. These subjects probably represent a subset of individuals at a greater risk of the development of overt HAM/TSP. Our data have indicated that urinary manifestations may occur even before a clinical picture of HAM/TSP is present.

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