

## REVIEW

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### URINARY AND SEXUAL MANIFESTATIONS OF PATIENTS INFECTED BY HTLV-I

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HTLV-I is considered to be a virus of low morbidity, since the principal diseases associated with this viral infection, HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T-cell leukemia/lymphoma (ATLL), are observed in less than 5% of infected individuals. Urinary symptoms are frequent in patients with myelopathy and consist principally of nocturia, frequency, urgency, and urinary incontinence; however, the importance of these dysfunctions and their correlation with myelopathy is still to be fully clarified. This review gives particular emphasis to the high frequency of urinary and sexual complaints not only in patients with myelopathy but also in individuals considered to be HTLV-I carriers. Detrusor overactivity and bladder-sphincter dyssynergia are the most common urodynamic findings. The fact that urinary complaints and urodynamic parameters reported in individuals considered to be carriers are similar to those detected in patients with myelopathy supports the hypothesis that urinary disorders may represent an oligosymptomatic form of HAM/TSP. Erectile dysfunction is frequently observed in HTLV-I-infected patients with or without myelopathy. Urinary tract infections are also highly prevalent in these patients. Despite the lack of an effective treatment for myelopathy, the use of anticholinergic drugs and phosphodiesterase type 5 (PDE5) inhibitors may improve urinary complaints and erectile dysfunction in these patients.

**KEYWORDS:** HTLV. Erectile dysfunction. Impotence. Urinary infection. Bladder. Urodynamics.

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#### INTRODUCTION

The human T-cell lymphotropic virus type 1 (HTLV-I) is a retrovirus of the Retroviridae family and the Oncovirinae subfamily. It is the etiological agent of HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP)<sup>1</sup> and of adult T-cell leukemia/lymphoma (ATL).<sup>2</sup> Around 20 million individuals worldwide are estimated to be infected with this virus, and of these, approximately 5% will develop ATL<sup>2</sup> or HAM/TSP.<sup>1</sup> Additionally, in our cohort at the HTLV-I clinic of the Hospital Universitário Professor Edgard Santos, up to 40% of HTLV-I-infected individuals have urinary manifestations, arthralgia or arthritis, sicca syndrome, chronic periodontitis, or erectile dys-

function. However, although other diseases are associated with HTLV-I, most individuals infected are considered to be asymptomatic carriers of the virus.

Central Africa, Japan, the Caribbean, South America, and Melanesia are the principal endemic areas for HTLV-I.<sup>3</sup> Although the viral infection is prevalent in Brazil and testing of blood products for HTLV-I has been mandatory since 1993, the level of knowledge of healthcare professionals with respect to the virus in general falls short of ideal.<sup>4</sup> The epidemiology of HTLV-I in Brazil is important, the infection being detected serologically in blood donors in every region of the country, and particularly in the states of Maranhão, Bahia, Pernambuco and Pará.<sup>5</sup> The highest seroprevalence in the country (1.8%) was found in the city of Salvador in the state of Bahia.<sup>6</sup> The same study found positive HTLV-I serology in 18.4% of patients hospitalized in an infectious disease unit. Another population-based study carried out in the same city reported a prevalence of 1.7% of infected individuals.<sup>7</sup> In Brazil, an alarming

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number of individuals (2,500,000) are believed to be infected by HTLV-I.<sup>8</sup> In the United States of America, 46,000 individuals are estimated to be infected with HTLV-I and 220,000 with HTLV-II.<sup>9</sup> In the city of Nagasaki, Japan, more than 10% of the adult population above 40 years of age is seropositive for HTLV-I.<sup>10</sup>

HTLV may be transmitted vertically (mother-to-child) through breastfeeding, and around 27% of newborn infants breast-fed for more than 3 months by seropositive mothers acquire the infection.<sup>4</sup> Intrauterine transmission and intrapartum transmission in the birth canal may occur in up to 5% of seropositive mothers.<sup>11</sup> Horizontal transmission occurs as a result of sexual intercourse with a seropositive individual, male-to-female transmission being the most frequent, as well as through blood transfusion and the use of injectable drugs via contaminated syringes or needles. Some investigators have reported that the infection acquired through a contaminated blood transfusion has been associated with the development of a more abrupt and intense state of myelopathy; however, others dispute this finding.<sup>3,4</sup> HTLV has lower infectivity and a longer incubation time than HIV.

Diagnosis of the infection is generally made following serological screening tests using the ELISA technique, positive cases being confirmed by Western blot (WB) or polymerase chain reaction (PCR) whenever WB is inconclusive. In Brazil, serological testing has been mandatory at all blood banks since 1993.

It is, therefore, important to acquire more knowledge about this viral infection, since its presence may be involved in several clinical findings associated with dermatological, rheumatological, neurological, ophthalmological, clinical, immunological, and urological disorders that result from seropositivity and HAM/TSP. In this review, emphasis is given to the urinary and sexual manifestations associated with HTLV-I infection, stressing the possibility of the existence of lesions to the medulla that may lead to an oligosymptomatic form of myelopathy caused by this virus.

### **Pathogenesis and clinical manifestations of HAM/TSP**

Around 5% of individuals infected by HTLV-I will go on to develop ATL or a progressive stage of inflammatory and demyelinating myelopathy known as HAM/TSP; its pathophysiology has not yet been completely clarified. Nevertheless, as in other diseases associated with HTLV-I, the immune response plays a fundamental role in this process. The predilection of the virus for T-lymphocytes is well known, although macrophages, B-lymphocytes, and other cells may also be infected by HTLV-I. In these cells, the Tax protein acts as a transactivator of cytokine-producing

genes, leading to a state of cell proliferation and the synthesis of various cytokines such as the interleukins IL-1, IL-2, IL-15, tumor necrosis factor alpha (TNF- $\alpha$ ), and interferon gamma (IFN- $\gamma$ ).<sup>12,13</sup> The expression of Tax protein on the surface of CD4<sup>+</sup> T cells leads to activation of cytotoxic CD8<sup>+</sup> T cells, which may destroy cells infected by the virus but also may contribute to an increase in the secretion of proinflammatory cytokines.<sup>14</sup>

Certain subtypes of HTLV-I have been reported to be associated with myelopathy.<sup>15</sup> In this context, it is possible that some virus subtypes may have a greater predilection for the central nervous system (CNS). Moreover, some studies have shown that the local production of chemokines such as CXCL9 and CXCL10 may recruit activated T cells, which after crossing the blood-brain barrier become installed predominantly in the thoracic medulla. The intense production of cytokines at CNS level would result in tissue damage.<sup>16</sup>

The majority of infected patients who develop HAM/TSP are between the ages of 30 and 40 years. Myelopathy generally evolves insidiously, but causes progressively significant damage to the CNS, and more than half of these individuals become wheelchair-dependent.<sup>17</sup> Lower back pain and paresthesias are common complaints in the initial stages of the disease, but diagnosis is only reached when the patient develops a change in gait associated with weakness and stiffening of the lower limbs (spasticity). Erectile dysfunction, sphincter disturbances, and urinary complaints also form part of the clinical picture. Physical examination registers an increase in lower limb reflex responses, clonus, and Babinski's sign. Progressive deterioration in walking leads to the use of aids such as a walking stick or a wheelchair.<sup>3</sup> In some patients, the disease develops in episodes similar to those seen in systemic sclerosis with which differential diagnosis has to be made in some cases.<sup>18</sup>

Other pathologies have also been described as being associated with HAM/TSP, such as infective dermatitis, uveitis, polyarthralgia, Sjögren's syndrome, alveolitis, and periodontitis.

### **Urinary Symptoms**

The most common urinary symptoms are increased urinary frequency, nocturia, urgency, dysuria, hesitancy, straining to urinate, sensation of incomplete emptying, and incontinence. In patients with classic myelopathy (HAM/TSP), the great majority report urinary symptoms, such as nocturia (81.4%), involuntary loss of urine (76.9%), urgency (74.4%), increased frequency (60.5%), and dysuria (39.5%). When evaluated regarding their quality of life with respect to their

urinary symptoms, 81% of patients with HAM/TSP reported that their quality of life was poor or very poor.<sup>19</sup>

In the early phases of bladder involvement, storage symptoms such as nocturia, urgency, and urge incontinence are more frequent. In later phases of the disease, the presence of bladder-sphincter dyssynergia leads to urinary voiding symptoms such as dysuria, hesitancy, straining to urinate, and sensation of incomplete voiding,<sup>20</sup> making intermittent bladder catheterization necessary. Some studies based on small series and case reports have suggested that urinary symptoms may constitute early manifestations of HTLV-I infection and may be the first sign of myelopathy. They may, therefore, be documented prior to the clinical neurological manifestations.<sup>21</sup> This fact has led us to investigate the frequency of urinary symptoms in individuals infected by HTLV-I who do not have HAM/TSP. Table 1 shows the frequency of symptoms in patients with HAM/TSP, and in HTLV-I carriers divided in 2 subgroups: those who had EDSS = 0 and those who had EDSS between 0.5 and 2. Note that the frequency of symptoms such as nocturia, frequency, dysuria, and urinary loss increases significantly as the degree of autonomy decreases as established by the Kurtzke scale (EDSS) in asymptomatic HTLV-I carriers (EDSS = 0) compared to oligosymptomatic patients (EDSS > 0 and < 2) and patients with myelopathy-HAM/TSP (EDSS ≥ 2), in a group of 218 patients.<sup>19</sup> As important as the high frequency of urinary complaints is the fact that the type of complaints was similar to those described in patients with HAM/TSP. This suggests the existence of a neurogenic bladder prior to the observation of other signs and symptoms that the medulla has been affected.<sup>21</sup> These data show that neurogenic bladder symptoms commonly seen in patients with HAM/TSP also constitute frequent

complaints in HTLV-I carriers. It is possible that these manifestations may represent a subclinical form of myelopathy and that some of these patients may go on to develop classic myelopathy.

Although frequency and nocturia are the most common urinary complaints, urinary incontinence is the symptom that causes the most profound effect on patients. Urinary incontinence may occur as a result of detrusor overactivity, low functional capacity, or stress incontinence due to hypermobility of the bladder neck or sphincter insufficiency. In a later phase, detrusor failure occurs with hypocontractility, high post-micturitional residue, and areflexia.<sup>20,22</sup> As many of these patients use antidepressant medication for the management of chronic pain, it is important to rule out the influence of these drugs on the detrusor muscle and urinary sphincter.

Treatment of bladder storage and voiding symptoms depends on the clinical status of the patient and the urodynamic findings. The use of anticholinergic medications such as propantheline bromide,<sup>23</sup> oxybutynin, and tolterodine may reduce urinary frequency and leakage resulting from detrusor overactivity. Patients with frequent urinary leakage, bladder/sphincter dyssynergia, or detrusor failure should undergo early bladder catheterization to protect the upper urinary tract and minimize leakage.

Since the urological manifestations presented by individuals infected by HTLV-I may be similar to those present in individuals with urinary tract infections (UTIs), an epidemiological, cohort study was carried out, based on information on urinary complaints but without carrying out urine culture.<sup>24</sup> Findings from this study showed urinary infection to be more frequent in HTLV-I seropositive patients than in seronegative controls, with an incidence ratio (IR) of 1.82 for kidney and bladder infection in HTLV-I carriers and 1.55 for patients infected by HTLV-II compared with seronegative controls.<sup>24</sup> Since urine culture was not carried out in this study, it is possible that a large number of these patients did not have a urinary infection but rather, urological complaints secondary to the medulla and bladder involvement seen in cases of HTLV-I infection. Nevertheless, HTLV-I-infected individuals would also be expected to have a higher frequency of urinary infections due to bladder dysfunction. In fact, in a series of 115 patients studied in our institution, urine culture-documented UTIs were observed in 14.7%. While the prevalence of UTI in asymptomatic carriers was 8.1%, in those with myelopathy, 43.3% had a positive urine culture.<sup>25</sup>

**Table 1** - Urinary symptoms in patients with HTLV-I

| Variable     | Asymptomatic carriers<br>EDSS = 0 | Subclinical myelopathy<br>EDSS > 0<br>and < 2 | HAM/TSP<br>EDSS ≥ 2 |
|--------------|-----------------------------------|---|---------------------|
| Nocturia     |                                   |   |                     |
| No           | 82.4%                             | 60%   | 18.6%               |
| Yes          | 17.6%                             | 40%   | 81.4%               |
| Incontinence |                                   |   |                     |
| No           | 86.6%                             | 72.7%   | 23.6%               |
| Yes          | 13.3%                             | 27.3%   | 76.9%               |
| Frequency    |                                   |   |                     |
| No           | 92.4%                             | 76.4%   | 39.5%               |
| Yes          | 7.6%                              | 23.6%   | 60.5%               |
| Urgency      |                                   |   |                     |
| No           | 91.6%                             | 76.4%   | 25.6%               |
| Yes          | 8.4%                              | 23.6%   | 74.4%               |
| Dysuria      |                                   |   |                     |
| No           | 92.4%                             | 85.5%   | 60.5%               |
| Yes          | 7.6%                              | 14.5%   | 39.5%               |

**Urodynamic Evaluation**

Urodynamic study is an important tool for the evalua-

tion of urinary dysfunction and is capable of detecting significant abnormalities in patients with HAM/TSP. The urodynamic findings in 4 different studies in patients with HAM/TSP are summarized in Table 2. The most frequent urodynamic finding in those patients is overactive detrusor, first described in 1989.<sup>26</sup> Cystometry, performed to evaluate patients in 2 studies carried out in Brazil, detected detrusor overactivity in 50%<sup>27</sup> and 80.76%<sup>28</sup> of patients, respectively. Nevertheless, in a study carried out in Japan, detrusor hypoactivity was the principal finding in the urodynamic evaluation.<sup>10</sup> Bladder-sphincter dyssynergia is also a frequent finding, detected in 29% to 34% of patients.<sup>10,27</sup> It should be emphasized that many patients with dyssynergia are also found to have detrusor overactivity at cystometry. We have also documented these urodynamic disorders in a sample of HTLV-I carriers who had urinary manifestations but do not fulfill the criteria for HAM/TSP.

**Table 2** - Urodynamic findings in patients with HAM/TSP\*

|                                  | Walton<br>1993 | Lima<br>2002 | Mori<br>2004 | Castro<br>2006 |
|----------------------------------|----------------|--------------|--------------|----------------|
| No. of patients                  | 5              | 26           | 32           | 34             |
| Detrusor overactivity            | 100%           | 80.7%        | 28.1%        | 50%            |
| Detrusor hypoactivity            | 0%             | 3.8%         | 65.6%        | 8.8%           |
| Bladder-sphincter<br>dyssynergia | 80%            | 34.6%        | 34.3%        | 29.4%          |
| Normal                           | 0%             | 15.4%        | 6.25%        | 5.9%           |

\*In some studies, the percentages may not add up to 100% due to an overlap of data or data not shown in this table. Only the urodynamic data of patients with HAM/TSP are shown in this table.

### Erectile Dysfunction

Erectile dysfunction (ED) is another condition that is very frequently found in patients with myelopathy. Nevertheless, despite its high prevalence, a literature search failed to find any publication on the subject in indexed journals. In a study carried out in our institution, we administered a questionnaire on sexual and erectile dysfunction and recorded a high prevalence of ED, with a global prevalence of 40.5% in a group of 79 patients, and a prevalence of 88.2% among those with HAM/TSP. Moreover, in patients without the formal criteria for diagnosis of HAM/TSP (EDSS between 0.5 and 2), a greater prevalence of ED was found compared to carriers with EDSS = 0. These results

were similar to findings in the group of patients with HAM/TSP, suggesting that in many patients, ED may be an early or initial manifestation of myelopathy.<sup>29</sup> In those individuals with ED but without HAM/TSP, discrete alterations may be seen in neurological status, as well as sphincter dysfunction and/or an increase in tendinous reflexes. The prevalence ratio of ED in the group of asymptomatic HTLV-I carriers with EDSS = 0 and the group with EDSS between 0.5 and 2 was 27.1.<sup>29</sup>

There has been a case report on a patient in whom ED manifested as the first symptom of HAM/TSP.<sup>30</sup> In the evaluation of HTLV-I seropositive men, we observed some cases of patients who develop severe ED at a young age, in most cases prior to serological diagnosis of HTLV. Some of these individuals go on to develop HAM/TSP, and this has been the target of intense research in our institute, since these patients may have early immunological responses.

The findings presented here reinforce the concept that urological manifestations, both urinary and sexual, may represent an earlier stage of the development of HAM/TSP, and urologists in regions in which HTLV-I is endemic should be alerted to this possibility. Although in many cases ED is severe, we have achieved excellent erectile response in clinical practice with the use of phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, and vardenafil) in patients who have had no sexual activity for months due to lack of an erection sufficient for penetration.

### CONCLUSIONS

Urinary symptoms are very common in HTLV-I carriers. Nocturia, increased frequency, detrusor overactivity, urinary incontinence, bladder-sphincter dyssynergia, and urinary infections as well as ED are the most common findings in this group of patients. It is important to add that such urinary tract symptoms and ED may represent the earliest signs of myelopathy. Therefore, patients in geographical regions with a high prevalence of HTLV having ED and/or detrusor overactivity of undetermined cause should be investigated with regard to the possibility of HTLV-I infection. Moreover, all urologists should be familiar with HAM/TSP, especially those living in regions that are endemic for HTLV-I, because early intervention in the course of this viral disease improves the quality of life of patients and may prevent more severe urinary tract lesions.

**RESUMO**

Oliveira P, Castro NM de, Carvalho EM. Manifestações urinárias e sexuais em pacientes infectados pelo HTLV-I. *Clinics*. 2007;62(2):191-6.

O HTLV-1 é considerado um vírus de baixa morbidade sendo a mielopatia associada ao HTLV-1 (HAM/TSP) e a leucemia / linfoma de células T do adulto (ATL) as principais doenças associadas à infecção viral, observados em menos de 5% dos indivíduos infectados. Manifestações urinárias são freqüentes em pacientes com mielopatia, e representadas principalmente por noctúria, polaciúria, urgência e incontinência urinária, embora a importância destas alterações, e a correlação com a patologia medular não tem sido devidamente estudada. Nesta revisão enfatizamos a elevada freqüência de queixas urinárias e sexuais em pacientes, não apenas os portadores de mielopatias, mas também em indivíduos considerados como portadores assintomáticos do HTLV-I. Hiperatividade detrusora e

dissinergia vesico-esfincteriana são as manifestações urodinâmicas mais freqüentes. A documentação de queixas urinárias e os achados urodinâmicos observados em indivíduos considerados portadores assintomáticos são semelhantes aos detectados em pacientes com mielopatia dão suporte à hipótese que alterações urinárias possam representar uma forma oligossintomática da HAM/TSP. Disfunção eréctil é freqüentemente observada em pacientes infectados pelo HTLV-1, com ou sem mielopatia. Infecção do trato urinário também tem elevada prevalência nestes pacientes. A despeito da ausência de um tratamento efetivo da mielopatia, o uso de anticolinérgicos e de inibidores da fosfodiesterase tipo 5 podem melhorar as queixas urinárias e a disfunção eréctil destes pacientes.

**UNITERMOS:** HTLV. Disfunção eréctil. Impotencia. Infecção urinária. Bexiga. Urodinâmica.

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