Isolated Bladder Dysfunction in Human T Lymphotropic Virus Type 1 Infection

Marcus Tulius Silva,1 Francisco Coutinho,2 Ana Cláudia Leite,1 Ramza Cabral Harab,1 Abelardo Araújo,1 and Maria José Andrada-Serpa1

1Instituto de Pesquisa Clínica Evandro Chagas, Fundação Oswaldo Cruz, and
2Serviço de Urologia do Hospital Municipal Souza Aguiar, Rio de Janeiro, Brazil

Neurogenic bladder is common in patients with human T lymphotropic virus type 1 (HTLV-1)–associated myelopathy/tropical spastic paraparesis (HAM/TSP). Here, we describe isolated neurogenic bladder dysfunction in HTLV-1–infected individuals without HAM/TSP and show that HTLV-1 proviral load is higher in such patients than it is in asymptomatic carriers. We suggest that testing for HTLV-1 antibodies should be performed for patients with neurogenic bladder of unidentified etiology.

Bladder dysfunction is a very common complaint, especially among women. Even after a comprehensive investigation, an etiologic cause cannot be determined in a considerable number of patients. HTLV-1, which is a retrovirus that is endemic in Japan, South and Central America, and Africa, is associated with different clinical conditions. Although HAM/TSP is the neurological disease that is most often associated with this retrovirus [1], other neurological conditions have also been associated with it; this recently led to the development of a broader, unified concept of a true HTLV-1 neurological complex [2]. Although bladder dysfunction is a common complaint in patients with HAM/TSP, it is not seen in neurological asymptomatic carriers (AC) [3]. We describe neurogenic bladder dysfunction in HTLV-1–infected individuals who do not fulfill the diagnostic criteria for HAM/TSP and show that the HTLV-1 proviral load in these individuals is higher than the loads in ACs and is similar to the loads in patients with HAM/TSP.

Patients and methods. Since 1992, we have been searching for neurological and clinical abnormalities in HTLV-1–infected individuals. All patients at our institution (Instituto de Pesquisa Clínica Evandro Chagas; Rio de Janeiro, Brazil) systematically undergo neurological and clinical examinations. Neurogenic bladder dysfunction is one of the syndromes investigated. Only patients with urinary incontinence and/or retention, abnormal findings of urodynamic studies, and normal findings of a neurological examination were considered to have isolated neurogenic bladder dysfunction associated with HTLV-1 (INBH).

An urologist (F.C.) examined all individuals with urinary symptoms and excluded alternative causes for bladder dysfunction. HTLV-1 proviral load in peripheral blood leukocytes was determined by real time PCR (SmartCycle; Cepheid) in all patients with INBH, 197 patients with HAM/TSP, and 97 ACs. The HTLV-1 proviral load was measured using the TaqMan system (Applied Biosystems). Standard curves were generated by amplification of a β-globin gene fragment from HTLV-1–negative genomic DNA and the HTLV-1 Tax region (tax gene) fragment from a cell line containing a single copy of HTLV-1 provirus (TARL-2). PCR was performed using 200 ng of DNA with 12.5 μL of TaqMan 2× universal PCR master mix (Applied Biosystems), 15 pmol of pX primers, 50 pmol of β-globin primers, and 2.5 pmol of the fluorescent probes, for a total volume of 25 μL. The HTLV-1 proviral load was calculated as follows: number of copies/100 cells = [taxcopies/(β-globincopies/2)] × 100. The lower limit of detection for the assay was 1 copy per 1 × 10^4 cells. We used a nonparametric test (Mann-Whitney U test) for statistical analysis.

Results. A total of 231 of 713 HTLV-1–infected individuals did not have HAM/TSP (i.e., were ACs). In this group, 12 (5.2%) presented with bladder dysfunction. Two of these patients were excluded (because of prostatic hyperplasia and vesicle prolapse). INBH was diagnosed in the remaining 10 HTLV-1–infected individuals (4.3%). The median length of urinary symptoms was 61.4 months (range, 42–114 months). Some patients were symptomatic for months before the HTLV antibody test was performed and a diagnosis was made (table 1). Urodynamic studies disclosed underactive detrusor in 4 patients and detrusor sphincter dyssynergia in 5 patients (table 1).

A urodynamic study was not performed for 1 patient who was lost to follow-up. The median proviral load was 8.7 copies per 100 leukocytes in the INBH group, 5.4 copies per 100 leukocytes in the HAM/TSP group, and 1.1 copies per 100 leukocytes in the AC group. There was a statistically significant difference between the mean proviral loads of patients with...
Discussion. We describe isolated bladder dysfunction in 10 of 231 HTLV-1–infected individuals without HAM/TSP who had normal findings of neurological examinations, and we demonstrated that HTLV-1 proviral load was higher in this group than in the AC group and was similar to levels observed in patients with HAM/TSP.

Bladder dysfunction is a very common complaint, particularly among women. It is also frequently observed in patients with HAM/TSP, and it sometimes heralds the gait disturbance [2]. Bladder dysfunction in patients without HAM/TSP has been described by Castro et al. [4]. However, in that study, the authors used the Expanded Disability Status Scale to classify patients as myelopathic or nonmyelopathic. According to the authors, patients with an Expanded Disability Status Scale score of up to 3 who did not fulfill clinical criteria for HAM/TSP were classified as nonmyelopathic HTLV-1 carriers. Expanded Disability Status Scale is a scale largely used to assess disabilities in patients with multiple sclerosis. This scale quantifies disability in several functional systems, such as motor, sensory, visual, and bowel and bladder systems. An Expanded Disability Status Scale score of 3 indicates moderate disability in 1 functional system or mild disability in 3 or 4 functional systems. According to the methodology used by Castro et al. [4], it is not possible to ensure that the findings of neurological examinations were normal and that patients do not present with a subclinical myelopathy. Also, HTLV-1 proviral load was not quantified in the study by Castro et al. [4]. In our study, we performed detailed neurological examinations, and any abnormalities were detected. Furthermore, a high proviral load observed in patients with INBH points to a possible relationship between HTLV-1 infection and neurogenic bladder dysfunction.

Bladder dysfunction in HAM/TSP is mainly characterized by dysynergia or underactivity of the detrusor muscle. This muscle receives motor innervations from cells of the intermediolateral columns of the gray matter from the second to the fourth sacral segments of the spinal cord (the detrusor center). Inflammatory lesions in the lateral columns along the thoracic and lumbosacral segments of the spinal cord could be responsible for both the urinary dysfunction and the pyramidal syndrome seen in patients with HAM/TSP. Theoretically, a discrete inflammatory reaction induced by HTLV-1 infection and restricted to sacral segments could be the cause of isolated bladder dysfunction without the pyramidal syndrome typically observed in patients with HAM/TSP.

The majority of HTLV-1–infected individuals remain asymptomatic throughout their lives. The factors that determine who will develop a neurological condition are still unknown. Apparently, proviral load has an important role in the pathogenesis, given that patients with HAM/TSP and those with other neurological conditions have a proviral load that is higher than that of ACs [5]. The role of a high proviral load in the pathogenesis of HTLV-1–associated diseases is supported by the relationship between virus expression and the specific immune response. HTLV-1–specific cytotoxic T lymphocytes attack and destroy infected CD4+ cells [6]. Nonetheless, this inflammatory response might result in damage to the nervous system. Therefore, a high proviral load might overstimulate HTLV-1–specific cytotoxic T lymphocytes, driving their immune response to harmful levels. Our data reinforce the role of HTLV-1 proviral load in the neuropathogenesis of HTLV-1 and the relationship between isolated bladder disturbances and HTLV-1 infection.

Although we cannot exclude the possibility that these individuals will experience progression to full-blown HAM/TSP in the future, we believe that a close follow-up is of utmost importance. This is an important issue, because early diagnosis and treatment is pivotal in HTLV-1–associated diseases: im-

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Table 1. Characteristics of patients with isolated neurogenic bladder dysfunction associated with human T lymphotropic virus type 1 (HTLV-1).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, years</th>
<th>HTLV-1 proviral load, copies per 100 leukocytes</th>
<th>Transmission</th>
<th>Urodynamic study</th>
<th>Duration of confirmed HTLV-1 infection, months</th>
<th>Duration of symptoms, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>13141</td>
<td>F</td>
<td>39</td>
<td>12.81</td>
<td>Breast-feeding</td>
<td>Detrusor sphincter dyssynergia</td>
<td>115.6</td>
<td>102</td>
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<tr>
<td>15354</td>
<td>F</td>
<td>57</td>
<td>6.76</td>
<td>Sexual</td>
<td>Underactive detrusor</td>
<td>67.4</td>
<td>66</td>
</tr>
<tr>
<td>17045</td>
<td>F</td>
<td>22</td>
<td>10.47</td>
<td>Breast-feeding</td>
<td>Detrusor sphincter dyssynergia</td>
<td>52.2</td>
<td>42</td>
</tr>
<tr>
<td>20639</td>
<td>F</td>
<td>50</td>
<td>15.34</td>
<td>Sexual</td>
<td>Underactive detrusor</td>
<td>10.8</td>
<td>44</td>
</tr>
<tr>
<td>18235</td>
<td>M</td>
<td>38</td>
<td>0.19</td>
<td>Sexual</td>
<td>Detrusor sphincter dyssynergia</td>
<td>35.9</td>
<td>54</td>
</tr>
<tr>
<td>19428</td>
<td>F</td>
<td>39</td>
<td>7.10</td>
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<td>Detrusor sphincter dyssynergia</td>
<td>23.2</td>
<td>54</td>
</tr>
<tr>
<td>18032</td>
<td>F</td>
<td>51</td>
<td>8.88</td>
<td>Sexual</td>
<td>Underactive detrusor</td>
<td>54.6</td>
<td>48</td>
</tr>
<tr>
<td>17477</td>
<td>F</td>
<td>43</td>
<td>8.58</td>
<td>Blood transfusion</td>
<td>Underactive detrusor</td>
<td>44.9</td>
<td>42</td>
</tr>
<tr>
<td>20517</td>
<td>F</td>
<td>21</td>
<td>8.86</td>
<td>Breast-feeding</td>
<td>Not performed</td>
<td>11.5</td>
<td>114</td>
</tr>
<tr>
<td>20546</td>
<td>M</td>
<td>59</td>
<td>1.11</td>
<td>Sexual</td>
<td>Detrusor sphincter dyssynergia</td>
<td>9.9</td>
<td>54</td>
</tr>
</tbody>
</table>

* From date of first positive ELISA and Western blot test results.

INBH and ACs (P < .001). The mean proviral loads in the INBH group and the HAM/TSP group were similar (P = .26).
munomodulatory or anti-inflammatory medications are the main therapeutic options in HAM/TSP, but such drugs should be given in the initial phases of the disease to avoid a more ominous progression to cord atrophy [7]. Therefore, the prompt detection of HTLV-1 antibodies in patients with neurogenic bladder of unknown etiology would allow the introduction of early therapy aimed at improving clinical symptoms and avoiding progression of the disease. We observed that some of our patients were symptomatic for months before an anti-HTLV antibody test was performed. Thus, we suggest that testing for HTLV-1 antibodies should be done soon in the preliminary investigation for patients with neurogenic bladder dysfunction of unknown etiology.

In summary, HTLV-1 can be associated with isolated bladder dysfunction. HTLV-1 proviral load is higher in patients with bladder dysfunction than it is in ACs. Testing for HTLV-1 antibodies should be included in the laboratory investigations for patients with bladder dysfunction of indeterminate cause who are from areas in which HTLV-1 is endemic. Clinicians in general should be aware of this association to improve early serologic diagnosis and treatment.

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