Clinical Characteristics of Patients in Peru with Human T Cell Lymphotropic Virus Type 1–Associated Tropical Spastic Paraparesis

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Background. Human T cell lymphotropic virus type 1 (HTLV-1) is associated with tropical spastic paraparesis (TSP). Peru is an area of endemicity for HTLV-1.

Methods. All patients with suspected cases of TSP referred to our institute (Institute of Tropical Medicine Alexander von Humboldt, Lima, Peru) from 1989 through 2002 were interviewed and tested for HTLV-1. All patients with positive results were evaluated by an expert physician. Disease progression was defined as “rapid” if the time between TSP onset and inability to walk unaided was <2 years.

Results. Among 165 patients enrolled, the symptoms and signs most frequently found were spasticity (in 97.5% of patients), hyperreflexia (95.4%), lower limb paresthesia (90.2%), pyramidal signs (82.6%), urinary complaints (82.0%), and lumbar pain (79.0%). Rapid progression was present in 21.5% of patients; mean age at TSP onset was higher among these patients than among slow progressors (P < .001). Severe spasticity, diminished vibratory sensation, and tremor were found more frequently among rapid progressors, compared with slow progressors.

Conclusions. HTLV-1—associated TSP is frequently diagnosed in areas of HTLV-1–endemicity. A subgroup of patients experiences rapid disease progression.

Infection with human T cell lymphotropic virus type 1 (HTLV-1) is a global epidemic affecting ~10–20 million people [1]. Although HTLV-1 infection remains asymptomatic in the majority of patients, it is also associated with several clinical conditions, such as adult T cell leukemia/lymphoma [2], Strongyloides stercoralis hyperinfection [3], crusted scabies [4], uveitis [5], and tropical spastic paraparesis (TSP) [6]. Mani et al. [7] introduced the term “tropical spastic paraparesis” in 1969 to designate a chronic, progressive paraparesis of unknown cause observed in tropical areas. The association between HTLV-1 and TSP varies between geographical regions: in a recent study [8], 87% of TSP cases in Columbia were found to be HTLV-1 seropositive, and 55%–65% of TSP patients in Peru were found to carry HTLV-1. The cumulative lifetime risk of developing TSP for HTLV-1—infected individuals has been estimated to range from 0.25% to 4% [9], although the risk of developing TSP appears to be higher in Latin America than in Japan [9, 10].

The major histopathological characteristic of TSP is a chronic inflammation of the white and gray matter of the spinal cord followed by a degenerative process that affects preferentially the white matter in the lower thoracic spinal cord [11]. The typical clinical description of TSP is that of a gradually appearing, symmetrical paraparesis with signs of pyramidal tract involvement that progresses slowly and without remission [12]. A minority of patients, however, experience rapid progression of their neurological symptoms [13], a phenomenon that has been associated with higher age at onset [14], parenteral HTLV-1 transmission [15], high provirus loads [16], and high antibody titers [16].

Peru is an area of endemicity for HTLV-1; the prev-
alence of the infection among blood donors, pregnant women, and healthy adult women in several parts of the country ranges from 1% to 3% [10, 17–20]. Since 1989, the Institute of Tropical Medicine Alexander von Humboldt in Lima, Peru, has been a national reference center for patients with HTLV-1 infection and associated diseases. We report on demographic and clinical characteristics of a series of patients with HTLV-1–associated TSP.

PATIENTS AND METHODS

Setting. Our study was conducted at the Institute of Tropical Medicine Alexander von Humboldt, in which the Department of Infectious Diseases, Tropical Medicine, and Dermatology of the Hospital Nacional Cayetano Heredia is located. Since 1989, patients with a presumptive diagnosis of TSP have been regularly referred to our institute from 3 major public hospitals in Lima.

Procedures. For all patients willing to participate, a blood sample for HTLV-1 and HTLV-2 testing was drawn at the first visit, and a questionnaire was administered by trained health workers. The information collected included demographic data, risk factors for HTLV-1 infection, and symptoms related to TSP and other HTLV-1–associated diseases. All HTLV-1–positive patients had appointments with an expert physician who corroborated the diagnosis of TSP according to the clinical criteria proposed by the World Health Organization [21]. Clinical data regarding disease progression were assessed at the first and subsequent visits. The routine laboratory package included ELISA tests (Sanofi-Pasteur or Cambridge); in patients with positive ELISA results, a Western blot test (Dupont) was performed for confirmation. HTLV-1–positive patients with a clinical diagnosis of TSP who were referred to our institute during the period July 1989–March 2002 were included in the analysis. Patients who had scarce information in their charts were excluded from the study. Informed consent was obtained at the first visit. We divided the participants into 2 groups on the basis of the pace of disease progression. If the time between the first lower limb symptoms and the inability to walk without 2 walking sticks was <2 years, we defined the patients as having rapid disease progression. All other patients were defined as having slow disease progression.

Statistical analysis. Data were stored and analyzed with SPSS software, version 10.0, for Windows; χ² and Fisher’s exact tests were used for comparison of categorical variables, and Student’s t test was used for continuous variables.

RESULTS

During the study period, 184 patients were diagnosed with HTLV-1–associated TSP; 19 were excluded because of scarce clinical information, and 165 were enrolled in the study. None of the patients had test results positive for HTLV-2.

The mean age (± SD) at the time of the first visit was 51.5 ± 12.4 years, and the mean age (± SD) at disease onset was 45.3 ± 12.6 years. One hundred and twenty (73%) of 165 patients were women (ratio of women to men, 8:3). The ethnic background was 64% Mestizo (105 of 164 patients) and 30.5% Quechua (50 of 164 patients); there were also 4 patients of African origin and 1 patient of Asian origin (table 1).

Among 143 patients for whom information on breast-feeding was available, 139 (97.2%) had been breast-fed; 72 (93.5%) of 77 subjects who knew the duration of breast-feeding had received it for >6 months. A history of blood transfusions was present in 47 (29.4%) of 160 patients. HTLV-1 infection was not related to transfusion in 7 patients, each of whom had exhibited TSP symptoms or had given birth to HTLV-1–positive children before the date of transfusion. The remaining 40 patients (25.0%) could have contracted HTLV-1 through blood transfusion. The mean time between blood transfusion and the onset of symptoms in these patients was 12.9 ± 11.4 years; of these patients, 19 (55.9%) of 34 developed symptoms within 10 years after transfusion.

One hundred and three (65%) of 158 patients had received intramuscular injections regularly before disease onset, and 86 (55.1%) of 156 had undergone ≥1 surgical procedure. History of sexually transmitted diseases (STDs) or genital ulcers was reported by 20 (45.5%) of 44 men; among women, 11 (10.1%) of 109 had a history of STDs or genital ulcers. Twenty-eight (27%) (105 women noted that a cautery of the cervix had been performed, which is, among gynecologists in Peru, a common procedure to treat chronic vaginal discharge. Forty-one (30%) of 135 patients reported a history of family members with paretic neurological problems, and 6 (4.4%) of 136 had relatives who had had leukemia or lymphoma (table 1).

The symptoms and signs most frequently encountered in this patient series were spasticity (155 [97.5%] of 159), hyperreflexia (145 [95.4%] of 152), lower limb paresthesia (111 [90.2%] of 123), other pyramidal signs (clonus and/or Babinski sign; 137 [92.6%] of 148), urinary complaints (123 [82.0%] of 150), lumbar pain (113 [79.0%] of 143), constipation (115 [77.7%] of 148), diminished vibratory sensation (72 [61.5%] of 117), and Hoffman sign (52 [40.6%] of 128) (table 2). The most frequent urinary complaints were difficulty both at starting and maintaining urination, incontinence due to urine overflow, and frequent urinary tract infections. Severe involvement of the urinary tract was the main reason for consultation in 4 patients. All 4 patients developed severe obstructive uropathy before the onset of TSP; 1 of them had undergone unilateral nephrostomy before HTLV-1 infection and TSP were diagnosed.

In 3 patients, the neurological findings were atypical at disease onset. One patient presented to the hospital with left hemiparesis, another had encephalitis-like clinical features, and a
third had flaccid quadriparesis; within months, all developed the typical signs and symptoms of TSP.

At their first visit, 56 (36.1%) of 155 patients were able to walk unaided, and 99 (63.9%) needed help or were not able to walk at all. Among the latter patients, 50 (52.6%) of 95 used a walking stick, 32 (33.7%) of 95 used a wheelchair, and 13 (13.7%) of 95 were bedridden; data were not recorded for 4 patients.

Thirty-four (21.5%) of 158 patients were classified as having experienced rapid disease progression (i.e., inability to walk unaided within the first 2 years after TSP onset), and 124 (78.5%) were classified as having experienced slow progression. The mean age at disease onset among patients with rapid progression of TSP was higher than that among slow progressors (51.9 years vs. 43.5 years; $P<.001$). With respect to ethnic background, all 4 patients of African origin had rapid progression (table 1). There were also differences in clinical presentation between the 2 groups: severe spasticity, diminished vibratory sensation, and intentional tremor were found more frequently among patients with rapid progression (table 2).

### DISCUSSION

This report is the summary of a sustained effort in collecting epidemiological and clinical information for patients with HTLV-1–associated TSP at our institution over the past 14 years. Seventy-three percent of the patients in this series were women (ratio of women to men, 8:3). This is consistent with other reports about HTLV-1 infection in general and TSP in particular [12, 22]; female predominance has also been recognized in the World Health Organization diagnostic guidelines for TSP [21]. The ethnic background of 31% of our patients was Quechua, which reflects the high prevalence of HTLV-1 among this population [18].

More than 95% of our patients were breast-fed for >6 months. In Peru, breast-feeding is a very common practice and is probably the main route of HTLV-1 transmission. HTLV-1 is also a sexually transmitted disease [23]. Studies in Peru have shown HTLV-1 prevalence rates in commercial sex workers to be 7%–25% [19, 24, 25]. It is noticeable that 45% of men and 10% of women admitted that they had had an STD or genital ulcer and that 27% of women reported that a cauterization of

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**Table 1. Demographic characteristics and history of patients with tropical spastic paraparesis according to disease progression.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with rapid progression (n = 34)</th>
<th>Patients with slow progression (n = 124)</th>
<th>All patients (n = 165)</th>
<th>$P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first visit, mean years ± SD</td>
<td>53.1 ± 10.3</td>
<td>51.0 ± 12.8</td>
<td>51.5 ± 12.4</td>
<td>.4</td>
</tr>
<tr>
<td>Age at disease onset, years</td>
<td>51.9 ± 9.9</td>
<td>43.5 ± 12.7</td>
<td>45.3 ± 12.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>25–70</td>
<td>15–75</td>
<td>15–75</td>
<td></td>
</tr>
<tr>
<td>&gt;50 years old</td>
<td>23/34 (67.6)</td>
<td>40/122 (32.8)</td>
<td>65/162 (40.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>26/34 (76.5)</td>
<td>90/124 (72.6)</td>
<td>120/165 (72.7)</td>
<td>.8</td>
</tr>
<tr>
<td>Men</td>
<td>8/34 (23.5)</td>
<td>34/124 (27.4)</td>
<td>45/165 (27.3)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mestizo</td>
<td>18/34 (52.9)</td>
<td>82/123 (66.7)</td>
<td>105/164 (64.0)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1/34 (2.9)</td>
<td>3/123 (2.4)</td>
<td>4/164 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Quechua/Andean</td>
<td>11/34 (32.4)</td>
<td>37/123 (30.1)</td>
<td>50/164 (30.5)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0/34</td>
<td>1/123 (0.8)</td>
<td>1/164 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Afro-Peruvian</td>
<td>4/34 (11.8)</td>
<td>0/123</td>
<td>4/164 (2.4)</td>
<td>.002</td>
</tr>
<tr>
<td>Received breast-feeding</td>
<td>24/25 (96.0)</td>
<td>108/111 (97.3)</td>
<td>139/143 (97.2)</td>
<td>.6</td>
</tr>
<tr>
<td>Received blood transfusion$^b,c$</td>
<td>4/32 (12.5)</td>
<td>35/118 (29.7)</td>
<td>40/157 (25.5)</td>
<td>.08</td>
</tr>
<tr>
<td>History of sexually transmitted disease</td>
<td>5/29 (17.2)</td>
<td>23/117 (19.7)</td>
<td>31/153 (20.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Family member with paralytic disorder</td>
<td>7/27 (25.9)</td>
<td>33/102 (32.4)</td>
<td>41/135 (30.4)</td>
<td>.7</td>
</tr>
<tr>
<td>Family member with leukemia/lymphoma</td>
<td>3/28 (10.7)</td>
<td>2/102 (2.0)</td>
<td>6/136 (4.4)</td>
<td>.07</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. of patients with the characteristic/no. of patients with existing data (percentage), unless otherwise indicated:

- $^a$ Comparison between patients with rapid and slow progression; Yates corrected $\chi^2$ test, Fisher’s exact test, and Student’s $t$ test.
- $^b$ Description of events before the onset of TSP.
- $^c$ Three women with HTLV-1–positive children born before transfusion were excluded.
- $^d$ Ethnic background was defined as Quechua if both parents were born in the Andean highlands and/or spoke Quechua language.
Table 2. Clinical characteristics of patients with tropical spastic paraparesis at first visit according to disease progression.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients with the specified characteristic/no. of patients with existing data. (%)</th>
<th>With rapid progression (n = 34)</th>
<th>With slow progression (n = 124)</th>
<th>All (n = 165)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weaknessb</td>
<td></td>
<td>32/33 (97.0)</td>
<td>113/114 (99.1)</td>
<td>152/154 (98.7)</td>
<td>.4</td>
</tr>
<tr>
<td>Hyperreflexiab</td>
<td></td>
<td>30/33 (90.9)</td>
<td>110/113 (97.3)</td>
<td>145/152 (95.4)</td>
<td>.1</td>
</tr>
<tr>
<td>Other pyramidal signsb,c</td>
<td></td>
<td>30/32 (93.8)</td>
<td>100/109 (91.7)</td>
<td>137/148 (92.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paresthesiab</td>
<td></td>
<td>24/27 (88.9)</td>
<td>83/92 (90.2)</td>
<td>111/123 (90.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Lumbar pain</td>
<td></td>
<td>20/27 (74.1)</td>
<td>87/109 (79.8)</td>
<td>113/143 (79.0)</td>
<td>.7</td>
</tr>
<tr>
<td>Spasticityb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td>2/32 (6.3)</td>
<td>29/120 (24.2)</td>
<td>33/159 (20.8)</td>
<td>.04</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>13/32 (40.6)</td>
<td>50/120 (41.7)</td>
<td>65/159 (40.9)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td>7/32 (21.9)</td>
<td>10/120 (8.3)</td>
<td>18/159 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Severity not specified</td>
<td></td>
<td>9/32 (28.1)</td>
<td>28/120 (23.3)</td>
<td>39/159 (24.5)</td>
<td></td>
</tr>
<tr>
<td>Diminished vibratory sensationb</td>
<td></td>
<td>18/21 (85.7)</td>
<td>52/91 (57.1)</td>
<td>72/117 (61.5)</td>
<td>.03</td>
</tr>
<tr>
<td>Intentional tremor</td>
<td></td>
<td>10/26 (38.5)</td>
<td>10/93 (10.8)</td>
<td>21/124 (16.9)</td>
<td>.002</td>
</tr>
<tr>
<td>Hoffman signd</td>
<td></td>
<td>8/23 (34.8)</td>
<td>39/98 (39.8)</td>
<td>52/128 (40.6)</td>
<td>.8</td>
</tr>
<tr>
<td>Urinary complaints</td>
<td></td>
<td>28/33 (84.8)</td>
<td>89/110 (80.9)</td>
<td>123/150 (82.0)</td>
<td>.8</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>28/32 (87.5)</td>
<td>83/110 (75.5)</td>
<td>115/148 (77.7)</td>
<td>.2</td>
</tr>
</tbody>
</table>

a Comparison between patients with rapid disease progression and those with slow disease progression, by Yates corrected *χ*² test and Fisher’s exact test.
b Symptom or sign in the lower extremities.
c Babinski and/or clonus.
d Stretch reflex in which the examiner snaps with his thumb nail on the nail of the patient’s middle finger; the sign is positive if the patient makes a grasping movement with the thumb and the index finger.

the cervix had been performed. We were unable to assess the impact of these infections on HTLV-1 transmission among our cases, but recently, a Peruvian report [26] has shown that chronic cervicitis is associated with shedding the virus. The promotion of condom use in sexual risk groups could be an effective method to reduce HTLV-1 transmission [24, 25].

Risk of infection with HTLV-1 after transfusion of whole blood has been estimated to range from 40% to 60% [27]. The high rate of blood transfusion among our patients (29%) was similar to that of a Brazilian cohort [12]. Such a high rate could imply that transfusion was an important source of infection in our cases. It is remarkable that the mean incubation time in patients with TSP and a history of blood transfusion was only 13 years, but transfusion was not related to more-rapid progression. In areas of endemicity, blood donors should be screened systematically for HTLV-1; Peru was the first Latin American country to adopt this measure, in 1999 [28]. There are communications from other areas of endemicity that report a 16% decrease in TSP cases only 2 years after the implementation of blood donor screening [29].

Associations between certain human leukocyte antigen alleles and TSP have been reported, and it has been proposed that a major gene could predispose to HTLV-1 infection [30], which suggests the influence of genetic background on individual susceptibility to developing HTLV-1–associated diseases. Familial aggregation of leukemia/lymphoma, TSP, and other HTLV-1–associated diseases has been reported before [31]. In this context, it is worth mentioning that 30% of our patients mentioned paretic neurological disorders in their families and that as many as 4% had family members with leukemia/lymphoma.

The symptoms and signs most frequently encountered among our patients, such as spasticity, hyperreflexia, lower limb paresthesia, clonus and/or Babinski sign, urinary complaints, lumbar pain, constipation, and diminished vibratory sensation, are those previously reported in other case series [12, 22]. Urological problems are frequent among HTLV-1–infected patients and, in some cases, are the first sign of TSP or the main reason the patient seeks medical attention [32]. Accordingly, urinary complaints were very prominent in this series and included difficulties in initiating voiding, the need to exert external pressure over the lower abdomen to start urinating (or to maintain voiding in more-severe cases), and even complete urinary retention. Repeated urinary infections were also very common, probably reflecting disorders in bladder emptying, as detrusor-sphincter dyssynergy during micturition has been described in TSP patients [33].
Three of the patients of this series had atypical neurological signs at onset. There have been previous reports about atypical presentations of TSP at onset [34, 35] which have remarked on the need for considering TSP as a possible diagnosis for patients with neurological disorders in areas of HTLV-1–endemicity, not only among patients with typical signs and symptoms.

The progression of TSP is generally considered to be chronic and steady [14]. Nevertheless, we found that 22% of patients experienced rapid progression if 2 years between the onset of lower limb symptoms and the inability to walk unaided was used as a cutoff point. Among these patients, some presented with an even more accelerated course of disease, with as little as 6 months between onset of symptoms and the inability to walk unaided. Some reports have linked onset at older age with rapid course of the disease [14], which coincides with our findings. We could not assess antibody titers and provirus loads in this study, which are other factors previously reported in association with rapid progression [16]. Except for severe spasticity, diminished vibratory sensation, and intentional tremor (all of which were found more frequently in patients with rapid progression than in patients with slow progression), there were no other clinical differences between patients with rapid progression and those with slow progression.

Immunological disorders that are apparently related to HTLV-1, such as Sjögren syndrome, keratoconjunctivitis sicca, dermatitis, polymyositis, and uveitis, have been increasingly reported in the past few years, sometimes concurrently with TSP [36]. This coexistence reinforces the evidence of an immunological mechanism in the physiopathology of TSP. In a prospective study that was recently initiated at our institution, 13 TSP patients have thus far been identified with chronic complaints or findings consistent with either Sjögren syndrome or keratoconjunctivitis sicca (I. Rolando, personal communication).

This study has some limitations, mostly related to its design. For instance, limitations in recall were inevitable, as it was not uncommon for patients to come for their first visit to the hospital years after the onset of TSP, and certain issues, such as breast-feeding, were invariably distant life-events. Nevertheless, this study is valuable because it describes one of the largest case series in Latin America.

We conclude that TSP is an incapacitating disorder that is not infrequently diagnosed in reference hospitals in areas of HTLV-1–endemicity. Onset of the disease is sometimes atypical, and the clinical picture appears to be broader than previously thought, including urological and ophthalmologic manifestations. Because of poorly understood reasons (which merit extensive research), a subgroup of patients experiences rapid progression of disease. In addition, clinical research should focus on the therapeutic management of TSP, especially among those patients with rapid progression.

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References


