Clinical Presentation of Individuals With Human T-Cell Leukemia Virus Type-1 Infection in Spain

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**Background.** Although only 8%–10% of persons infected with human T-cell leukemia virus type 1 (HTLV-1) may develop virus-associated diseases lifelong, misdiagnosis of asymptomatic infected carriers frequently leads to late diagnoses.

**Methods.** A nationwide HTLV-1 register was created in Spain in 1989. A total of 351 infected persons had been reported by the end of 2017. We examined all new HTLV-1 diagnoses during the last decade and compared their clinical presentation.

**Results.** A total of 247 individuals with HTLV-1 infection had been reported in Spain since year 2008. The incidence has remained stable with 20–25 new diagnoses yearly. Women represented 62%. Only 12% were native Spaniards, most of whom were foreigners from Latin America (72.5%). Up to 57 (23%) individuals presented clinically with HTLV-1-associated conditions, including subacute myelopathy (n = 24; 42.1%), T-cell lymphoma (n = 19; 33.3%), or *Strongyloides stercoralis* infestation (n = 8; 14%). Human T-cell leukemia virus type 1 diagnosis had been made either at blood banks (n = 109; 44%) or at clinics (n = 138; 56%). It is interesting to note that Spaniards and especially Africans were overrepresented among patients presenting with HTLV-1-associated illnesses, suggesting that misdiagnosis and late presentation are more frequent in these populations compared to Latin Americans.

**Conclusions.** Given that 23% of new HTLV-1 diagnoses in Spain are symptomatic, underdiagnosis must be more common. Although screening in blood banks mostly identifies asymptomatic Latin American carriers, a disproportionately high number of Spaniards and Africans are unveiled too late, that is, they already suffer from classic HTLV-1 illnesses.

**Keywords.** adult T-cell leukemia; epidemiology; HTLV-1; myelopathy; screening.

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HTLV-1 infection diagnosed only during the last decade. Expert clinicians reviewed clinical charts and checked neurological and hematological signs/symptoms in particular. When possible, epidemiological information was tracked to determine the most likely routes of HTLV-1 transmission.

Statistical Analysis
All numerical variables are reported as absolute values and percentages. Categorical variables were compared using $\chi^2$ or Fisher exact tests, whereas noncategorical variables were compared using Student t test or Mann-Whitney U tests. All analyses were 2-tailed, and only $P$ values below .05 were considered to be significant. All statistical analyses were performed using SPSS software, version 16.0 (SPSS Inc., Chicago, IL).

RESULTS
A total of 247 individuals with HTLV-1 infection had been reported in Spain since 2008. Most cases were diagnosed around large urban areas (Madrid and Barcelona) where the largest immigrant populations live. Women represented 62%. Only 12% were native Spaniards, most of whom were foreigners from Latin America (72.5%). Africans represented 8.5%. It is interesting to note that heterosexual exposure is the most likely source of HTLV-1 infection among native Spaniards, in most cases this was linked to partners from endemic regions in Latin America.

During this period, 57 (23%) individuals presented clinically with HTLV-1-associated conditions, including TSP/HAM ($n=24$; 42.1%), ATL ($n=19$; 33.3%), and Strongyloides stercoralis infestation ($n=8$; 14%), or other potentially linked conditions, such as neuropathies, sicca syndrome, etc. In 4 (7%) of these symptomatic individuals, HTLV-1 was found as coinfection with human immunodeficiency virus-1.

One hundred nine subjects (44%) subjects were diagnosed with HTLV-1 at blood banks, and 138 (56%) subjects were diagnosed at clinics. As expected, blood donors with HTLV-1 infection were all asymptomatic, whereas 57 (41%) patients identified at clinics had HTLV-1-associated conditions at presentation.

The main characteristics of these 2 populations are recorded in Table 1. Spaniards and especially Africans were overrepresented among hospital-based HTLV-1 diagnoses, suggesting that late presentation and misdiagnosis were more common in these 2 groups compared with Latin Americans.

Table 2 records the main features of 57 HTLV-1-infected patients presenting with symptomatic illnesses, which were mostly neurological (61%) or hematological conditions (33%). Women were more frequently represented than men (65%), regardless of clinical presentation. On the other hand, individuals presenting with TSP/HAM were on average 8 years older than those with ATL. Finally, although Spaniards presented more frequently with TSP/HAM than ATL (8 vs 2), the opposite occurred among Africans (3 vs 5).

It is interesting to note that a 54-year-old woman developed rapid-onset subacute paraparesis after kidney transplantation in 2015 from a cadaveric donor retrospectively known to be HTLV-1 positive [13]. In contrast, the recipient of the second kidney experienced early graft rejection that required surgical removal. The recipient discontinued immunosuppressants, and more than 2 years later he remains asymptomatic despite having been infected with HTLV-1.

DISCUSSION
A total of 247 individuals with HTLV-1 infection have been diagnosed in Spain during the last decade. The large immigrant flow from HTLV-1-endemic regions mostly accounts for this population, although native Spaniards represent 12% of cases. Overall, the relatively large proportion of symptomatic individuals (23.1%) suggests that HTLV-1 infection is frequently underdiagnosed in Spain.

Screening in Spanish blood banks mostly identified asymptomatic Latin American carriers, whereas classic HTLV-1-associated conditions such as TSP/HAM and ATL unexpectedly unveiled a disproportionately high number of HTLV-1 infections among Spaniards and Africans. In native Spaniards, late HTLV-1 diagnoses could largely be due to poor clinical

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Blood Donors</th>
<th>Clinics</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>247</td>
<td>109 (44)</td>
<td>138 (56)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>153 (62)</td>
<td>69 (63)</td>
<td>84 (61)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>43.4</td>
<td>42.6</td>
<td>44</td>
<td>n.s.</td>
</tr>
<tr>
<td>Country of Origin (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Spain</td>
<td>29 (12)</td>
<td>9</td>
<td>20</td>
<td>.09</td>
</tr>
<tr>
<td>• Latin America</td>
<td>179 (72.5)</td>
<td>88</td>
<td>91</td>
<td>n.s.</td>
</tr>
<tr>
<td>• Africa</td>
<td>21 (8.5)</td>
<td>1</td>
<td>20</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>• Others</td>
<td>18 (7.3)</td>
<td>11</td>
<td>7</td>
<td>n.s.</td>
</tr>
<tr>
<td>HTLV symptomatic disease (%)</td>
<td>57 (23)</td>
<td>0</td>
<td>57 (41)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>HIV coinfection</td>
<td>4 (1.6)</td>
<td>0</td>
<td>4 (3)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; HTLV, human T-cell leukemia virus type 1; n.s., nonsignificant.
suspicion in persons that had acquired the virus locally after sexual contacts with Latin Americans [14, 15]. This finding supports that HTLV-1 should no longer be neglected, and testing should be promoted at clinics for sexually transmitted infections [16]. In Africans, limited access to health services along with poor clinical and epidemiological suspicion in persons coming from endemic regions might have contributed to frequent HTLV-1 misdiagnosis. Moreover, Africans are generally excluded in blood banks due to high rates of prior history of malaria and other tropical conditions. Therefore, they rarely would be identified as asymptomatic HTLV-1 blood donors.

More than half of new HTLV-1 diagnoses in Spain during the last decade were performed at clinics. Up to 41% of these patients had typical HTLV-1-associated illnesses, that is, either neurological or hematological conditions. Women were more frequently represented than men, regardless of clinical presentation. On average, individuals presenting with TSP/HAM were older than those with ATL. It is interesting to note that Spaniards more frequently presented with TSP/HAM than ATL, whereas Africans presented with ATL more often than with TSP/HAM. This finding is in agreement with the fact that HTLV-1-associated leukemias/lymphomas mostly develop in subjects infected perinatally from their mothers in highly endemic regions [17, 18]. Sexual transmission was by far the most likely route of HTLV-1 infection among native Spaniards.

To date, 4 individuals in the Spanish register had developed rapid-onset subacute myelopathy after solid organ transplantation from 2 separate donors retrospectively known to be HTLV-1-positive. The first organ donor was reported in year 2000. He was a young male Spaniard, asymptomatic, with a Venezuelan mother who most likely transmitted the infection perinatally. All 3 recipients of the 2 kidneys and the liver, respectively, developed TSP within 18 months [19]. The second donor was 1 male Spaniard, asymptomatic, who most likely acquired HTLV-1 via sexual contact with a Brazilian partner. Although one of the donor’s kidney recipients developed TSP [13], another one who experienced early organ rejection and discontinued immuno-suppressants has remained asymptomatic to date despite becoming infected with HTLV-1.

We should acknowledge several limitations of our study. First, given its retrospective study design, we could not be certain about the route of infection for a subset of individuals, and, likewise, some epidemiological information was missing. Second, given the voluntary reporting system, we could not totally exclude that some HTLV-1-positive persons diagnosed in Spain were not counted. However, we have a relatively good surveillance system, and we actively search and try to contact those doctors and departments where potential HTLV-1 cases or their relatives are medically attended.

**CONCLUSIONS**

In summary, our results show that the incidence of new HTLV-1 infections in Spain during the last decade has remained relatively stable at approximately 20–25 cases per year. Although Latin Americans and Africans represent more than 80% of cases, 12% of new HTLV-1 diagnoses are native Spaniards. Moreover, Spaniards represent approximately 20% of all symptomatic HTLV-1 diagnoses. Altogether, late presentation and misdiagnosis should encourage wider HTLV-1 testing in Spain. Lessons from Spain may well apply to other countries with similar large immigration flows from Latin America. Human T-cell leukemia virus screening should be particularly favored in the following populations: (1) blood donors, given the relatively high number of Latin Americans coming from HTLV-1-endemic regions; (2) solid organ transplantation, given the frequent and high risk of rapid clinical progression [20, 21]; and pregnant women, given that perinatal HTLV-1 transmission to newborns can be effectively avoided if breastfeeding is discouraged [15].

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**Table 2. Main Features of 57 Patients Presenting with HTLV-1 Symptomatic Illnesses in Spain (2008–2017)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>TSP/HAM</th>
<th>ATL</th>
<th>Others*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>24 (42.1)</td>
<td>19 (33.3)</td>
<td>14 (24.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Female gender (n)</td>
<td>17</td>
<td>11</td>
<td>10</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>52.1</td>
<td>44.6</td>
<td>49.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Country of Origin (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Latin America</td>
<td>13</td>
<td>12</td>
<td>11</td>
<td>n.s.</td>
</tr>
<tr>
<td>• Africa</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>n.s.</td>
</tr>
<tr>
<td>• Spain</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>n.s.</td>
</tr>
<tr>
<td>• Others</td>
<td>0</td>
<td>0</td>
<td>1b</td>
<td>n.s.</td>
</tr>
<tr>
<td>HIV coinfection (n)</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Abbreviations: ATL, adult T-cell leukemia/lymphoma; HAM, human T-cell leukemia virus-associated myelopathy; HIV, human immunodeficiency virus; HTLV, human T-cell leukemia virus type 1; N, number; n.s., nonsignificant; TSP, tropical spastic paraparesis.

*Strongyloides stercoralis infestation (8), neuropathies other than TSP/HAM (6), sicca syndrome (3), etc.

bRomania.
References


