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BRIEF REPORT

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 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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Human T-cell leukemia virus type 1 (HTLV-1) was the first discovered human retrovirus. It was isolated 50 years ago from a patient with a cutaneous T-cell lymphoma [1]. Approximately 10–15 million people are estimated to be chronically infected with HTLV-1 worldwide [2, 3]. Highly endemic regions exist in the Caribbean and parts of Latin America, West Africa, Iran, Japan, and Romania. Within the European Union, most HTLV-1 infections are made in persons with black ethnicity from coming from either the Caribbean or sub-Saharan Africa [2–4]. The virus is mostly transmitted sexually [5], perinatally by breastfeeding [6], and parenterally throughout contaminated blood either after transfusions or needle sharing among injection drug users [7, 8].

Only 8%–10% of persons infected with HTLV-1 may develop 2 characteristic-associated diseases [9–11]—namely, tropical spastic paraparesis (TSP), or HTLV-associated myelopathy (HAM), and adult T-cell leukemia/lymphoma (ATL)—during their lifetime. Misdiagnosis of asymptomatic HTLV-1 carriers frequently leads to late diagnoses. In this regard, the real burden of HTLV-1 infections in a region may be indirectly inferred from the number of people presenting with symptomatic illnesses.

METHODS

A nationwide HTLV-1 register and biological repository was created in Spain since 1989. More than 45 centers are members of the Spanish HTLV Network, distributed across the whole national geography. Participating centers and major epidemiological findings have already been described elsewhere [12]. Uniform case report forms collecting demographics, epidemiological features, clinical signs, and manifestations are filled out for each new diagnosis by the respective doctor in charge. On a yearly basis, a group meeting is arranged around mid December and new cases are presented and discussed by all members of the network.

Human T-cell leukemia virus testing in Spain is conducted at the microbiology departments of clinics/hospitals on demand, only when there is clinical suspicion, and rarely as part of general screening for sexually transmitted infections or prenatal testing. In contrast, HTLV antibodies are examined mandatorily in all transplants as well as in at-risk blood donors. Individuals diagnosed with HTLV-1 at blood banks are initially informed by the transfusion center medical staff and invited to attend appointments with infectious diseases specialists that are associated with the Spanish network at clinics located at different large cities.

A total of 351 individuals with HTLV-1 infection had been reported in Spain by the end of 2017. For the purpose of this study, we examined the clinical presentation of all persons with

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 χ^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 1. New HTLV-1 Diagnoses in Spain (2008–2017)

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

Abbreviations: HIV, human immunodeficiency virus; HTLV, human T-cell leukemia virus type 1; n.s., nonsignificant.

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

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

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.

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

[b]Romania.

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 immunosuppressants 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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