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HIV co-infection in HTLV-1 carriers in Spain

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ABSTRACT

Background: Human retroviruses HIV and HTLV share transmission routes. HIV widely spread in Spain during the 80 s through injection drug use and sex, and nowadays HIV rates in Spain account for one of the largest in Europe. In contrast, HTLV-1 is not endemic in Spain, despite hosting huge numbers of migrants from highly endemic regions. Herein, we report the rate and main features of the HIV-HTLV co-infected population in Spain.
Methods: A national registry exists in Spain for HTLV since year 1989. Data from standardized case report forms and one centralized lab repository were reviewed, especially for the subset with HTLV-HIV co-infection.
Results: Up to December 2018, a total of 369 individuals with HTLV-1 had been diagnosed in Spain. 64% of the population were females, and Latin American individuals accounted for 64.5%. Classical HTLV-associated illnesses were found in 12.7% (myelopathy) and 7.6% (leukemia).

HIV coinfection was found in 12 (3.2%). Of those, 3 patients (25%) were female and 39 (75%) were of non-Spanish origin. All but two harbored HIV-1 subtype B, being non-B variants found in the two West Africans. Exposure had been sexual in most cases, being 4 homosexual men. Seven HTLV-HIV co-infected patients had developed AIDS and two had developed myelopathy. There was no evidence for increased HTLV-1 clinical pathogenicity due to HIV coinfection.
Conclusion: HIV coinfection is infrequent (< 5%) among HTLV-1 carriers in Spain. More than half of co-infected patients come from Latin America. Sexual contact is the most frequent risk behavior, being MSM one third of cases. Late diagnosis explains the high rate (9/12) of clinical manifestations in our HIV-HTLV co-infected population.

1. Introduction

Human retroviruses HIV and HTLV share transmission routes, including sexual, vertical and parenteral exposure. Although HIV widely spread in Spain during the 80 s through injection drug use, men having sex with men (MSM) are mostly driving new incident HIV infections nowadays (Soriano et al., 2018). More than 140,000 HIV-positive persons are currently living in Spain (47 million total population), which represents one of the largest HIV rates in Europe (Soriano et al., 2018).

In contrast, HTLV-1 is not endemic in Spain, with 20–25 new cases diagnosed every year. Of note, more than half are migrants coming from highly endemic countries, mostly in Latin America, Sub-Saharan Africa and Romania (de Mendoza et al., 2017). HTLV-1 misdiagnosis seems to be frequent in Spain, due to lack of clinical suspicion and scarce testing. As a result, HTLV-1 is frequently found in patients first presenting with clinical symptoms, either tropical spastic paraparesis (TSP) or adult T-cell lymphoma (ATL) (de Mendoza et al., 2017).

Co-infection with HIV and HTLV-1 has been recognized mostly in individuals with risk behaviors living in highly endemic regions. Interactions at cellular level have been investigated since both viruses infect preferentially CD4 + T lymphocytes (Casoli et al., 2007). Hypothetically, a rise in dysfunctional CD4 + T lymphocytes due to HTLV-1 might convey a false sense of immune competence in HIV co-infected individuals. Furthermore, conflicting results have been reported for

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increased neurological manifestations, enhanced progression to AIDS and transmission rates (Brites et al., 2009; Tulius Silva et al., 2009; Paiva et al., 2017). Herein, we report the rate and main features of the HIV-HTLV-1 co-infected population in Spain.

2. Patients and methods

A national registry exists in Spain for HTLV since year 1989. More than 50 labs/clinics across the Spanish geography belongs to the network. Data from standardized case report forms and one centralized lab repository are discussed in one open meeting arranged annually. More information on this network has been reported elsewhere (de Mendoza et al., 2017).

We retrospectively identified the subset of individuals with HTLV-1 that had anti-HIV antibodies. Main demographics, clinical manifestations, and laboratory findings were examined separately and compared with the rest of the HTLV-1 population. Most diagnosis of HIV plus HTLV-1 coinfection had been concurrent, since all new HTLV-1 diagnosis are tested for HIV. In contrast, HTLV-1 is generally not part of the wider routine HIV lab screening information requests in Spain.

2.1. Statistical analysis

All numerical variables are reported as absolute values and percentages. Categorical variables were compared using $\chi 2$ or Fisher exact tests whereas non-categorical variables were compared using Student *t* test or Mann-Whitney *U* tests. All analyses were 2-tailed and only *p* values below 0.05 were considered as significant. All statistical analyses were performed using SPSS software version 16.0 (SPSS Inc, Chicago, IL).

3. Results

Up to December 2018, a total of 369 individuals with HTLV-1 had been diagnosed in Spain. More than 60% (n = 223) had been identified during the last decade. Mean age was 50 years, 64% were female; and 64.5% were Latin Americans. Classical HTLV-associated illnesses were found in 12.7% (TSP) and 7.6% (ATL).

HIV coinfection was found in 12 individuals (3.2%). Table 1 summarizes the main features of the HIV-HTLV-1 co-infected population. 75% were male, and only 3 (25%) were Spaniards, being the majority of patients from Latin America (Venezuela, Peru, Ecuador and Colombia). All but two harbored HIV-1 subtype B, being non-B variants found in the two West Africans, that originally came from Ghana and Equatorial Guinea. There were no cases of HIV-2. Exposure to HIV and HTLV-1 had been sexual in most cases; four were homosexual men. Two thirds of the coinfected population had been diagnosed before 2010.

Compared with HTLV-1-monoinfected individuals, HIV-HTLV-1 co-infected patients were more frequently younger, homosexual men, and presented with AIDS (Table 2). Overall, seven HTLV-HIV-HTLV-1 co-infected patients had developed AIDS and two had developed TSP. Of note, most individuals with AIDS developed opportunistic infections before triple antiretroviral therapy became available or presented with late diagnosis. In a subset of 5 individuals coinfected with HIV and HTLV-1, mean HTLV-1 proviral load was low and did not differ from other asymptomatic non-coinfected HTLV-1 carriers (data not shown).

Ten out of 17 diagnosis of AIDS-defining conditions in the whole HTLV-1 Spanish register developed in HIV-negative persons. Immune dysfunction associated with HTLV-1 could account for this observation. AIDS-defining conditions in this subset of HTLV-1-positive/HIV-negative individuals referred to recurrent pneumonia, extrapulmonary tuberculosis, and esophageal candidiasis.

Table 2
Main features of the HTLV-1 population according to HIV status.

	Total	HIV-pos	HIV-neg	p
No.	369	12	357	
Female gender (n, %)	227 (63.6)	3	224	0.07
Mean age (years)	50	43	52	0.03
Transmission route:				
• Heterosexual	113 (30.6)	5	110	ns
• Homosexual	6 (1.6)	4	3	0.04
• Others	12 (3.3), 30 (8.1),	1 (IDU)	11/30/	< 0.01
(IDU/vertical/transfusion/ transplant)	10 (2.7), 5 (1.4)		10/5	
• Unknown	193 (52.3)	2	191	ns
Region of origin:				ns
• Latin America	238 (64.5)	7	231	
• Africa	41 (11.1)	2 (EG, G)	39	
• Spain	65 (17.6)	3	62	
• Others	10 (2.7)	0	10	
• Unknown	15 (4.1)	0	15	
HTLV-associated illnesses:				ns
• TSP/HAM	48 (12.7)	2	46	
• ATL	28 (7.6)	0	28	
• AIDS	17 (4.6)	7	0	
• Others	10 (2.7)	0	10 (SS)	
• None (asymptomatic)	266 (72.1)	3	273	
Year of diagnosis (< or ≥ 2010)	146 vs 223	8 vs 4	138 vs 219	ns

IDU, injection drug use; ATL, adult T-cell leukemia/lymphoma; TSP/HAM tropical spastic paraparesis/HTLV-associated myelopathy.

4. Discussion

Despite being the first identified human retrovirus (Poiesz et al., 1980), HTLV-1 infection remains a neglected disease, even when 10–15 million people are infected worldwide (Gessain and Cassar, 2012). Both

Table 1
Major features of the HIV-1 and HTLV-1 coinfected population.

No.	Diagnosis year*	Diagnosis place	Country of origin	Gender	Age (years)	Transmission route	HTLV illnesses	HIV illnesses	CD4 count	Comments
1	1992	Santiago	Spain	male	unknown	MSM	no	AIDS	?	–
2	1996	Santiago	Spain	male	35	HTX	no	AIDS	?	–
3	2002	Orense	Venezuela	male	37	unknown	no	AIDS	?	CNS toxoplasma
4	2003	Madrid	Equatorial Guinea	male	31	HTX	no	AIDS	?	
5	2005	Madrid	Spain	male	35	IDU	no	no	?	–
6	2008	Madrid	Ecuador	male	35	MSM	no	AIDS	?	–
7	2009	Madrid	Peru	male	?	HTX	no	AIDS	95	–
8	2009	Zaragoza	Peru	female	38	unknown	HAM/TSP	no	359	CNS Cysticercosis
9	2010	Madrid	Ecuador	male	52	MSM	no	no	?	–
10	2012	Zaragoza	Ghana	female	51	HTX	no	AIDS	73	PCP
11	2013	Malaga	Ecuador	male	39	MSM	no	no	?	–
12	2017	Menorca	Colombia	female	61	HTX	HAM/TSP	no	89	–

CNS, central nervous system; PCP, Pneumocystis carinii pneumonia; IDU, injection drug use; MSM, men having sex with men; HTX, heterosexual *Diagnosis for HTLV-1.

HIV and HTLV-1 share transmission routes, being nowadays sexual contact far more frequent than parenteral or vertical exposures. However, in contrast with HIV, less than 10% of HTLV-1 carriers may go to develop clinical manifestations in their life. Furthermore, no pandemic resembling the one caused by HIV-1 has occurred with HTLV-1. This virus is relatively confined to highly endemic regions split globally, with foci in Japan, the Caribbean, Latin America, Sub-Saharan Africa, Iran and Romania (Gessain and Cassar, 2012). In other parts of the world, HTLV-1 diagnoses often have been identified and/or tracked to immigrants from highly endemic regions. For this reason, HIV and HTLV-1 coinfections have been only occasionally reported outside HTLV-1 endemic areas and thereby HTLV screening is not mandatory in HIV persons in Western countries (Rossheim et al., 2016).

In Spain, immigration from Latin America and the Caribbean has been significant during the last two decades, favored by longstanding cultural close relationships. Data from the International Organization for Migration (www.iom.int) reported 5,852,953 individuals from Latin America living in Spain in 2015, which represented 12.7% of the total 47 million population in the country. The figure for Latin Americans was 1,567,034 (26.8% of migrants). Based on these numbers and taking into account the specific places of birth, estimates for HTLV-1 immigrants in Spain have been produced, roughly in the range of 15,000–47,000 (De Mendoza et al., 2019a). It should be noted that these figures must be considered as underestimates, since second wave transmissions from migrants to natives that occur locally are disregarded using this inference method. Likewise, HTLV-1 persons coming from highly endemic regions other than Latin America are disconsidered.

It is the lack of clinical suspicion and the fact that HTLV-1 diagnosis is only requested occasionally in clinics, which explain the large HTLV-1 misdiagnosis rate in Spain. No doubt that pushing the awareness on this infection among both doctors and risk populations will unveil a large number of asymptomatic HTLV-1 carriers (De Mendoza et al., 2019b).

Being the number of HIV-infected persons high in Spain (estimates of 140,000) and overlapping transmission routes for both HIV and HTLV-1, it is noteworthy that we found HIV co-infection in less than 5% of HTLV-1 carriers in Spain. Not surprisingly, however, more than half of co-infected patients came from Latin America. Sexual contact was the most frequent risk behavior, being MSM one third of cases.

It is noteworthy that the HIV coinfection rate drastically differs in HTLV-1 compared to HTLV-2 carriers in Spain. Up to December 2018, 803 persons with HTLV-2 infection had been reported at the Spanish register, of whom 83% were HIV-positives (it was 3% for HTLV-1). Furthermore, most HTLV-2 carriers in Spain were former injection drug users (76%) and native Spaniards instead of foreigners (73%).

The high rate (9/12; 75%) of clinical manifestations in our HIV-HTLV coinfected population, with 7 AIDS cases and 2 individuals with TSP, was significant. Instead of a hypothetical enhanced bi-directional pathogenicity, late diagnosis most likely would explain our findings. The importance of early diagnosis is clear for HIV, since earlier antiretroviral therapy initiation may halt progression to AIDS in carriers and more importantly avert new HIV transmissions. Unfortunately, late HIV diagnosis is still relatively frequent in Spain, particularly among immigrants, including those from Latin America, which are disproportionately represented among new HIV diagnoses (Soriano et al., 2018; Ndumbi et al., 2018).

For HTLV-1, at this time earlier diagnosis may permit reducing transmissions, either vertical or sexual, but there is no way to prevent disease development, that occurs in roughly 10% of carriers, either as paraparesis or leukemia/lymphoma. Despite close similarities between viral enzymes, attempts to reduce HTLV-1 replication with antiretroviral drugs used to treat HIV-1 have produced disappointing results (Treviño et al., 2012; Kuhnert et al., 2014; Dhasmana and Taylor, 2014). At this time, monitoring proviral load and periodic clinical assessment would be the only helpful recommendation. Individuals with infection of more than 4% of their peripheral blood mononuclear cells are at increased risk for developing TSP or ATL. As with other chronic viral infections, such as HIV, hepatitis B or hepatitis C, HTLV-1 carriers show elevated immune activation and inflammatory markers (Brites et al., 2018) that ultimately may lead to an increased risk for cardiovascular disease (Abolbashari et al., 2018). Therefore, healthy preventive lifestyle, including exercise and stop smoking should be encouraged.

In summary, HIV coinfection is recognized in less than 5% of HTLV-1 carriers in Spain. More than half of dually infected patients are Latin Americans, and sexual risk behaviors are the most likely source of viral infections. Late diagnosis explains the high rate of clinical manifestations in our HIV-HTLV co-infected population, presenting with either AIDS (seven) or HTLV-1 subacute myelopathy (two).

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