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HTLV-1-associated myelopathy in Spain

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ABSTRACT

Background: HTLV-1 infection is a neglected disease. Over 10 million people are infected worldwide, with hot spots of high endemicity across all continents. Roughly 5% of HTLV-1 carriers develop HTLV-1-associated myelopathy (HAM), a progressive subacute neurological disabling disease.
Methods: We report the main features of patients diagnosed with HAM up to date in Spain, a non-endemic country with a relatively high migrant flow from Latin America and Equatorial Africa, where HTLV-1 is endemic.
Results: A total of 451 cases of HTLV-1 had been recorded in Spain until the end of year 2022. HAM had been diagnosed in 58 (12.9%). The current incidence is of 2–3 new cases per year. Women represent 76%. Mean age at diagnosis is 49 years-old. Nearly 60% are Latin Americans. Although sexual transmission is the most likely route of HTLV-1 acquisition, up to 6 individuals had been infected following solid organ transplantation. Rapid onset myelopathy developed in all but one of these transplant recipients from three HTLV-1-positive donors. HTLV-1 subtype 1a transcontinental was the only variant recognized in HAM patients. HTLV-1 proviral load was significantly greater in HAM patients than in asymptomatic HTLV-1 carriers (677 vs 104 HTLV-1 DNA copies/10^4 PBMC; $p = 0.012$). Symptom relief medications and physiotherapy have been the only treatment providing some benefit to HAM patients. Neither significant clinical nor virological efficacy was noticed using antiretrovirals in at least 9 HAM patients. Two thirds of HAM patients ended up in a wheelchair and with urinary/fecal sphincter incontinence.
Conclusion: HAM is the most frequent clinical manifestation of HTLV-1 infection in Spain, a non-endemic country. Middle aged women migrants from Latin America are the most frequently affected. Two thirds end up in a wheelchair despite using antiretroviral therapy.

1. Introduction

Infection with HTLV-1 is a neglected condition, despite being the second most prevalent human retroviral infection worldwide after HIV-1. Current estimates are of 10 million people living with HTLV-1 globally, with high endemic regions located in Equatorial Africa, Latin America and the Caribbean, northeastern Iran, southwestern Japan and Australia [1,2]. Once acquired, either sexually, vertically or parenterally, HTLV-1 infection is lifelong. Although many HTLV-1-infected individuals are asymptomatic and unaware of their infection, roughly 10%

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will go to develop clinical manifestations, generally after several decades of silent infection, being the most characteristic HTLV-1-associated myelopathy (HAM) and adult T-cell leukemia/lymphoma (ATLL) [3,4].

HAM was originally reported in Martinique, a French overseas territory in the Caribbean region, in patients with tropical spastic paraparesis, in whom seroreactivity to specific anti-HTLV-1 antibodies was unveiled [5]. HAM is a neuroinflammatory subacute disease of the spinal cord. Patients with HAM typically experience chronic lower back pain with early neuropathic urinary bladder symptoms followed by the development of lower limb spasticity [6,7]. Proximal weakness of the lower limbs, which eventually spreads distally, is common. Acute and subacute presentations, with progression to severe paraplegia within a few months, can occur. Poorer prognostic indicators in patients with HAM include a high HTLV-1 proviral load, female sex, age at onset of 50 years or older, and an early rapid clinical progression [8,9].

Herein, we discuss the main features of patients diagnosed to date with HAM in Spain, a non-endemic country with a relatively high migrant flow from regions in Latin America and Equatorial Africa, where HTLV-1 is endemic.

2. Methods

A nationwide HTLV-1 register was created in Spain in 1989. Main demographics, clinical symptoms/signs and laboratory findings are collected for each new HTLV-1 case at baseline and longitudinally when possible, using a standardized case report form. Members of the Spanish HTLV Network cover nationwide most of the lab facilities where this virus can be diagnosed, including public or private microbiology labs or blood banks [10].

Notification of HTLV-1 positives to the national register is voluntary. However, from the coordination team, clinics are contacted when new cases are identified at the public National Hospital Discharge database and there is no prior recording at the HTLV-1 register [11,12]. Further details have been specified elsewhere [13]. Finally, provision of free access to diagnostic tools including HTLV-1 proviral load and subtyping, facilitates and ensure that almost all HTLV-1 cases in the country are recorded within 1–2 years upon first diagnosis. HTLV-1 proviral load was measured in all cases following Ficoll collection of PBMC from patient's blood. HTLV-1 subtyping was performed examining LTR sequences.

The diagnosis of HAM was made following international clinical, laboratory, electrophysiological and neuroimaging criteria [14]. Briefly, the most frequent symptom was lower limb motor dysfunction, followed by bladder/bowel dysfunction and sensory disturbance. Further classification of HAM patients according to the rapidity of clinical evolution was made, as recommended elsewhere, distinguishing rapid and slow progressors [15].

2.1. Statistical analysis

Figures are given in absolute numbers and percentages. Quantitative and qualitative variables are described as medians with interquartile ranges, mean with standard deviations or as proportions. Bivariate comparisons of quantitative variables were performed using the Chi^2 test, with Yates's correction when appropriate.

All statistical analyses were performed using the IBM SPSS package for Windows v25.0 (IBM Corp, Armonk, NY). All tests were two-tailed and only p values <0.05 were considered as significant.

2.2. Ethical approval

The study was designed as a multicentre and retrospective collection of anonymized and consecutive clinical data associated to serum HTLV-1 antibodies. It was approved by the International University of La Rioja (UNIR) ethics committee (ref. PI047/2023).

3. Results

The Spanish HTLV-1 network updates on a yearly basis the national figures for this viral infection and produces recommendations for screening and/or medical management. The 2022 annual meeting was held in Madrid on December 14th 2022. A total of 451 cases of HTLV-1 had been recorded in Spain until then. HAM had been diagnosed in 58 (12.9%). ATLL had been diagnosed in 35 (7.8%). The first case of HAM in Spain was reported in 1989, in a mission nun who had returned to Barcelona from a long stay in Peru, where she had received blood transfusions years earlier [16].

Fig. 1 depicts graphically temporal trends in HAM diagnoses reported in Spain over the last three decades. The current incidence of HAM in Spain is of 2–3 new cases per year. It has remained quite stable within the last 15 years.

Women represent 76% of HAM patients at the Spanish register (Table 1). Mean age at diagnosis was 49 years-old. Nearly 60% of HAM patients in Spain are migrants from Latin America. Sexual transmission was the most likely route of contagion in at least half of HAM patients. Reasonable exclusion for other routes (transfusions, transplants, and vertical exposure, as indirectly supported by disease in family members), were excluded in these cases. On the contrary, positive evidence for sex partners from HTLV-1 endemic regions was recorded. Compared to the rest of HTLV-1-infected individuals in Spain, patients with HAM were significantly more frequently female, older, born in Spain, and infected by sexual contact. Their mean HTLV-1 proviral load was also significantly greater (677 vs 104 HTLV-1 DNA copies/10^4 PBMC; $p = 0.012$), but with wide confidence intervals. HTLV-1 subtype 1a transcontinental was the most frequent genetic variant in our study population.

Up to 4 patients with HAM in Spain had presumably been infected vertically. All but one were Latin American women. Interestingly, the only native was a 64-years-old female born in the Canary islands that had been breastfed by a wet-nurse from Latin America. She had a slow progressive clinical form of HAM and high proviral load (1580 HTLV-1-DNA copies/10^4 peripheral blood mononuclear cells).

It is noteworthy that 6 individuals in our register, 5 of them with HAM, had been infected following solid organ transplantation (Table 2). All organ recipients were native Spaniards. Likewise, all three HTLV-1 positive organ donors were native Spaniards. However, either one of their parents or a sex partner were from HTLV-1 endemic regions and did not know their carrier status. All organ recipients received kidneys but one who received a liver. Interestingly, rapid onset myelopathy developed in all but one transplant recipient [17,18]. The only exception was a kidney recipient of a cadaveric HTLV-1 positive donor that experienced organ rejection. The transplanted kidney had to be removed and immunosuppressors were stopped. The recipient became infected with HTLV-1 but he did not develop neurological symptoms. He has remained on regular dialysis to date [19,20].

Symptom relief medications and physiotherapy have been the only treatment that gave some benefit to HAM patients. No significant clinical nor virological efficacy was noticed using antiretrovirals in at least nine of our HAM patients [21–23], including the subset of five rapid progressors with HAM after transplantation. Overall, two thirds of HAM patients on follow-up ended up in a wheelchair and with sphincter incontinence, after a mean follow-up of 7.2 ($\pm$ 3.4) years.

HIV-1 coinfection was recognized in 3 (5.2%) out of 58 HAM patients. All three were women born in Latin America. Two of them most likely had been infected by both HIV-1 and HTLV-1 throughout sexual contact. For the remaining case there was evidence for perinatal transmission from her mother (Table 3). All received antiretroviral therapy and experienced significant CD4+ T-cell gains. However, no significant clinical improvements were noticed in neurological symptoms/signs.

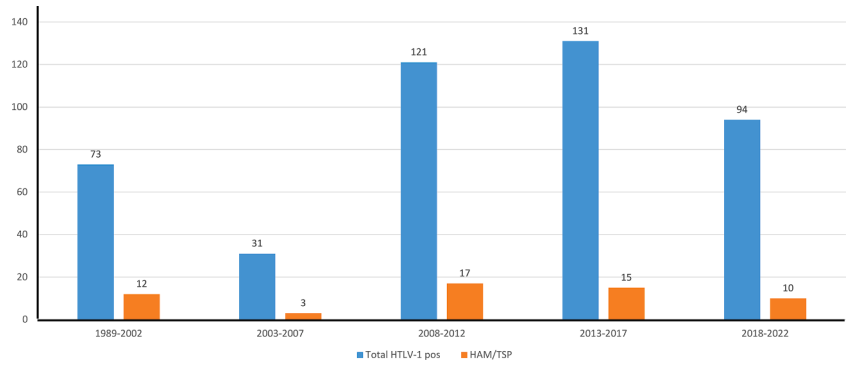

Fig. 1. Annual incidence of HAM in Spain.

Table 1
Main features of individuals with HTLV-1 infection in Spain.

	All HTLV-1	No HAM	HAM	p
N (%)	451	393	58	–
Female sex	286 (63.4)	242 (61.6)	44 (75.8)	0.035
Mean age (years)	43	40.5	49.1	0.003
Country of birth (n,%)	298 (66)	264	34 (58.6)	0.66
Latin America	74 (16.4)	(67.2)	17 (31.5)	0.0024
Spain	52 (11.5)	60 (15.3)	4 (6.9)	0.24
Africa		48 (12.2)		
City of residence (n,%)	144 (31.9)	128	16 (27.6)	0.45
Madrid	130 (28.9)	(32.6)	15 (25.9)	0.88
Barcelona	31 (6.9)	115	5 (8.6)	0.57
Zaragoza	18 (4)	(29.3)	4 (6.9)	0.23
Santiago	7 (1.5)	26 (6.6)	3 (5.2)	0.017
Bilbao		14 (3.6)		
		4 (1.1)		
Transmission route (n,%)	145 (32.1)	117	28 (48.3)	0.005
Heterosexual	45 (10)	(29.8)	4 (6.9)	0.4
Vertical	11 (2.4)	41 (12.2)	3 (5.2)	0.32
Transfusion	6 (1.3)	8 (2.0)	5 (8.6)	<0.001
Transplantation		1 (0.2)		
HIV-1 coinfection (n,%)	16 (3.5)	13 (3.3)	3 (5.2)	0.5
HTLV-1 subtype 1a (n,%) (*)	104	74	30	-
Transcontinental variant	87	61	26	-
Median HTLV-1 proviral load (copies/10^4 PBMC) (IQR) (**)	259 (37–1428)	104 (10–804)	677 (169–1767)	0.012

* 108 patients had been sequenced for HTLV-1 subtyping.
** Proviral load was available for 91 patients.

4. Discussion

HTLV-1 is an intracellular virus transmitted throughout body fluids, including blood, semen and milk. Accordingly, sexual exposure, breastfeeding, transfusions, needle sharing in drug users, etc. pose individuals at risk for contagion [1]. Global estimates for HTLV-1 infected individuals are of 10 million people, with hot spots distributed across all continents. High rates of HTLV-1 infection have been reported among aboriginal people in Australia, Equatorial Africa, Latin America and the Caribbean, northeastern Iran, and southwestern Japan [1,2,24].

Children born from infected mothers may acquire HTLV-1 when breastfeeding extends beyond 6 months, since protection given by passively transmitted mother's antibodies at birth protect the baby until then [25]. Following implementation of HTLV-1 antenatal screening in Japan, new infections in adolescent and adult generations throughout sexual contact have replaced vertical transmission as the main route for transmission. Being Japan a country of 125 million population, a recent survey estimated that roughly 3000 new HTLV-1 infections occur annually [26].

HTLV-1 is more efficiently transmitted sexually from male to female than vice versa. In contrast with HIV-1, men who have sex with men depict only slightly higher rates of HTLV-1 infection than heterosexuals [27]. Among the latest, the rate of infection increases with time of sexual relationships with an HTLV-1-infected partner [1,28].

Outside endemic regions, HTLV-1 infection is mostly diagnosed in migrants coming from countries with high HTLV-1 prevalence. Less frequently, HTLV-1 is found in natives that had lived in endemic countries or had sex partners from such regions. In our series of 58 patients diagnosed with HAM, up to 17 (31.5%) were native Spaniards.

Roughly 5% of HTLV-1 carriers develop HAM. The host's T-cell response primarily drives the risk of disease. HTLV-1 indirectly damages the central nervous system (CNS) through infecting CD4+ T cells, which cross the blood-brain barrier and activate cytotoxic CD8+ T cells,

Table 2
Solid organ transplant recipients infected with HTLV-1 in Spain*.

No.	Sex	Age (years-old)	Country of birth	Year of diagnosis	City living in Spain	HTLV-1 subtype	HTLV-1 proviral load (copies/10^4 PBMC)	Clinical manifestations
1	Female	53	Spain	2000	Bilbao	1a *transcontinental*	–	HAM
2	Male	55	Spain	2000	Bilbao	1a *transcontinental*	–	HAM
3	Female	44	Spain	2000	Bilbao	1a *transcontinental*	–	HAM
4	Male	49	Spain	2008	Barcelona	1a *transcontinental*	870	HAM
5	Male	64	Spain	2015	Zaragoza	1a *transcontinental*	25	Asymptomatic
6	Female	53	Spain	2015	Pamplona	1a *transcontinental*	305	HAM

* All three organ donors were native Spaniards, but have either a parent or a sex partner from HTLV-1 endemic regions.

Table 3
Patients with HTLV-1-associated myelopathy and HIV-1 coinfection.

No.	Sex	Age (years-old)	Country of birth	Year of HAM diagnosis	City living in Spain	Transmission route	HTLV-1 proviral load (copies/10^4 PBMC)	CD4+ T-cell count (cells/mm^3)
1	Female	38	Peru	2009	Zaragoza	sexual	1166	359
2	Female	61	Colombia	2017	Menorca	sexual	–	89
3	Female	39	Ecuador	2019	Santiago	vertical	–	166

causing neuroglial death and degeneration [29]. A high proviral load in the blood and even greater in the cerebrospinal fluid (CSF) are risk factors for developing HAM. The CSF concentrations of the cytokines neopterin and CXCL10 (IP-10) correlate with the rate of HAM disease progression. CXCL10 also drives chronic inflammation by stimulating the migration of infected T cells into the CNS [30]. Using magnetic resonance, images of cervical and upper thoracic spinal cord typically show extensive transverse myelitis in HAM patients [31].

We did not have the chance to study biomarkers, such as the CXCL10 and/or neopterin, in the blood or CSF of our HAM patients. Neither markers of neurodegeneration, such as neurofilament light chain, that may also help to predict HAM prognosis. Although in older studies we found evidence of an association of HAM with certain HLA and *IL28B* alleles in HTLV-1 carriers [32,33], their predictive value is low and clinically not relevant.

There is currently no cure for HAM. Interferon alpha has shown some therapeutic benefit in a randomized control trial [34], but the efficacy is limited, and the treatment is rarely used due to concerns on the side effects of the drug. Corticosteroids are presently the mainstay of therapy and are used to suppress inflammation and improve or maintain long-term neurologic function. Evidence for corticosteroids is, however, limited and largely based on observational series and clinical experience [35]. Choice of steroid therapy is based on the rapidity of onset and speed progression. In rapid HAM progressors, high-dose induction with methyl-prednisolone followed by prednisolone maintenance is usually advocated, while in slow HAM progressors, low-dose prednisolone may be solely used. This stratification of presentation type and corticosteroid therapy has been supported by a recent randomized trial that, in both groups, demonstrating an improvement in motor disability scores and walking distance [36].

Steroid-sparing, anti-inflammatory, disease-modifying maintenance treatment for HAM should be considered case by case where treatment with corticosteroids is not felt appropriate or where there is a need to wean off steroids due to complications. Early evidence from 19 HAM patients supported the use of mogamulizumab, an anti-CCR4 monoclonal antibody that targets infected cells, with reductions in spasticity in 79% and decreases in motor disability in 32% of HAM patients [37]. However, access to this drug remains limited to clinical trials and is not readily available. Furthermore, mogamulizumab has to be administered intravenously every 2 months and most patients develop rash, which is a limiting side effect. Although significant reductions in HTLV-1 proviral load are recognized in most treated patients, clinical neurological improvement is only seen in the subset of patients with a shorter time from the beginning of neurological manifestations. HAM patients with long-lasting disease and well-established paraparesis and urinary incontinence does not show any improvement [38,39]. Outside of immunomodulating therapy, the mainstay of management of HAM is supportive symptomatic relief medication and physiotherapy.

In summary, we collected information on 58 HAM patients diagnosed in Spain over three decades. They represented 13% of all individuals diagnosed with HTLV-1 in Spain to date. This overepresentation of neurological disease most likely reflects suboptimal HTLV-1 testing and underdiagnosis [40]. In the absence of any efficacious antiviral treatment or vaccine [41], HTLV-1 screening in non-endemic regions should be performed at least once in all migrants from endemic regions and in natives who had lived in or had sex partners from endemic countries, and before organ transplantation. Given the predominant sexual route of contagion, HTLV-1 testing should also be added into the screening list of persons attended for sexually transmitted infections [42]. Finally, since avoidance of breastfeeding largely halts vertical HTLV-1 transmission to newborns, HTLV-1 testing should be part of prenatal screening [43].

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Disclosures

The authors have completed the information regarding conflicts of interest in the requested documentation and have no conflicts of interest to disclose.

Ethical approval

UNIR ethics committee ref. PI047/2023.

CRediT author statement

VS and CdM conceptualized the work, CdM, VS and MJP wrote the first draft. All authors contributed with clinical data, and reviewed and edited the draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix

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