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Review

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HTLV-1 infection: An emerging risk. Pathogenesis, epidemiology, diagnosis and associated diseases

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ABSTRACT

The Human T-Lymphotropic Virus type 1 (HTLV-1) affects up to 10 million people worldwide. It is directly associated to one of the most aggressive T cell malignancies: Adult T Cell Leukemia-Lymphoma (ATLL) and a progressive neurological disorder, Tropical Spastic Paraparesis/ HTLV-1 Associated Myelopathy (TSP/HAM). Also, infected patients tend to have more severe forms of infectious diseases such as Strongyloidiasis and Tuberculosis. HTLV spreads through parenteral, sexual, and vertical (mother-to-child) routes. Effective viral transmission is produced mainly by cell to cell mechanism, unlike other retroviruses such as HIV, which usually spread infecting cells in a cell-free form. HTLV also has a peculiar distribution, with clusters of high endemicity in nearby areas of very low prevalence or absence of the virus. This could be explained by factors including a possible founder effect, the predominance of mother to child transmission and the cell-to-cell transmission mechanisms. More data on viral epidemiology are needed in order to develop strategies in endemic areas aimed at reducing viral dissemination. In this review, we critically analyze HTLV-1 pathogenesis, epidemiology, diagnosis, associated diseases, preventive strategies, and treatments, with emphasis to the emerging risk for Europe and particularly Spain, focusing on prevention methods to avoid viral transmission and associated diseases.

Keywords: HTLV-1, ATLL, HAM/TSP, Adult T Cell Leukemia Lymphoma, emerging risk, epidemiology, pathogenesis.

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Infección por HTLV-1: Una enfermedad emergente. Patogenia, epidemiología, diagnóstico y enfermedades asociadas

RESUMEN

El Virus Linfotrópico Humano T tipo 1 (HTLV-1) afecta hasta a 10 millones de personas en todo el mundo. Está directamente asociado a una de las neoplasias malignas de células T más agresivas: Leucemia-Linfoma de células T del Adulto (LLTA) y a un trastorno neurológico progresivo: Paraparesia Espástica Tropical / Mielopatía Asociada a HTLV-1 (PET/MAH). Además, los pacientes infectados tienden a tener formas más graves de enfermedades infecciosas como la Estrongiloidiasis y Tuberculosis. El HTLV se propaga a través de las siguientes vías: parenteral, sexual y vertical. La transmisión viral efectiva se produce principalmente por el mecanismo de contacto directo de célula a célula, a diferencia de otros retrovirus como el VIH, que generalmente se propaga infectando a las células mediante partículas virales libres. El HTLV-1 tiene una distribución peculiar, con grupos de alta endemicidad en áreas cercanas de muy baja prevalencia o ausencia del virus. Esto podría explicarse por factores que incluyen un posible efecto fundador, el predominio de la transmisión vertical (leche materna) y los mecanismos de transmisión por contacto célula a célula. Hoy en día se necesitan más datos epidemiológicos para desarrollar estrategias en áreas endémicas, destinadas a reducir la diseminación viral. En esta revisión, se analiza la patogénesis, la epidemiología, el diagnóstico, las enfermedades asociadas, las estrategias preventivas y los tratamientos del HTLV-1, con énfasis en el riesgo emergente para Europa y particularmente España, centrándonos en los métodos de prevención para evitar la transmisión viral y las enfermedades asociadas.

Palabras clave: HTLV-1, LLTA, MAH/ PET, Leucemia-Linfoma de células T del Adulto, riesgo emergente, epidemiología, patogénesis.

INTRODUCTION

HTLV-1 was the first retrovirus identified as an etiologic agent of human disease [1, 2]. This virus produces several malignancies including Adult T Cell Leukemia-Lymphoma (ATLL) and Tropical Spastic Paraparesis/ HTLV Associated Myelopathy (TSP/HAM) [3]. HTLV-1 spreads through parenteral, sexual, and vertical (mother-to-child) routes [4]. It shares similar routes of transmission with other viruses including HIV and HCV that are often associated in the same patients. There are four known types of HTLV: HTLV-1, HTLV-2, HTLV-3, and HTLV-4. HTLV-1 is the most pathogenic for humans while HTLV-2 usually produces mild neurological disease. Both are prevalent worldwide. HTLV-3 and HTLV-4 have been identified only in Central Africa and usually affect non-human hominids [4]. The striking geographical distribution of the virus through Japan, West Africa and Latin America-Caribbean regions is still an unresolved puzzle. This, together with the pathogenesis, epidemiology, diagnosis, associated diseases, preventive strategies and treatments will be critically analyzed in this review, highlighting the emerging risk for Europe, exemplified with the case of Spain, and the prevention strategies to avoid it.

HTLV-1 PATHOGENESIS

Viral structure and replication. HTLV-1 is a complex human retrovirus that belongs to *Deltaretrovirus* genus. Complex retroviruses, including lentiviruses such as HIV, have several proteins that require more complex transcriptional processing than the simple retroviruses [4]. This virus genome is composed by the retroviral genes *gag, pro, pol* and *env*, which encode some viral structural proteins [4]. The *gag* gene encodes the Matrix (MA), Capsid (CA) and Nucleocapsid (NC) proteins. The *pro* gene encodes a viral protease that is responsible of facilitating the maturation of viral particles. The *pol* gene encodes Reverse Transcriptase (RT), RNaseH (RH) and Integrase (IN). *Env* gene encodes gp46 Surface Unit (SU) and gp21 Transmembrane Unit (TU). Additionally, it has the pX region, that contains the genes of six viral accessory proteins: Tax, Rex, $p12^{I}$, $p13^{II}$/p8, $p30^{II}$ and Basic Zipper Factor (HBZ) protein [4].

HTLV-1 has two sense proviral genomic strands: a positive sense strand that encodes most of structural proteins, and a negative or antisense strand that encodes HBZ [4]. HTLV-1 frames contain two flanking long terminal repeat (LTR) sequences with three components: a unique 3′ (U3) region, a repeated (R) region, and a unique 5′ (U5) region (figure 1) [4]. HTLV-1 has mainly tropism for CD4+ cells, but can also infect CD8+ cells, B lymphocytes, dendritic cells, monocytes and endothelial cells [4]. HTLV-1 has the ability of attachment and fusion to the target cells. The attachment begins when surface subunit (SU) of the HTLV-1 envelope glycoprotein (Env) interacts with three cellular surface receptors: Glucose Transporter (GLUT1), Heparin Sulfate Proteoglycan (HSPG) and the VEGF-165 receptor Neuropilin-1 (NRP-1) [5]. These receptors are widely distributed on target cells [5].

Following attachment and fusion of the virus to the target cell, the viral RNA is delivered into the cytoplasm and is converted into double stranded DNA (dsDNA) through reverse transcription [5]. Then dsDNA is integrated into the host nuclear genome [5]. This provirus is transcribed by cellular RNA

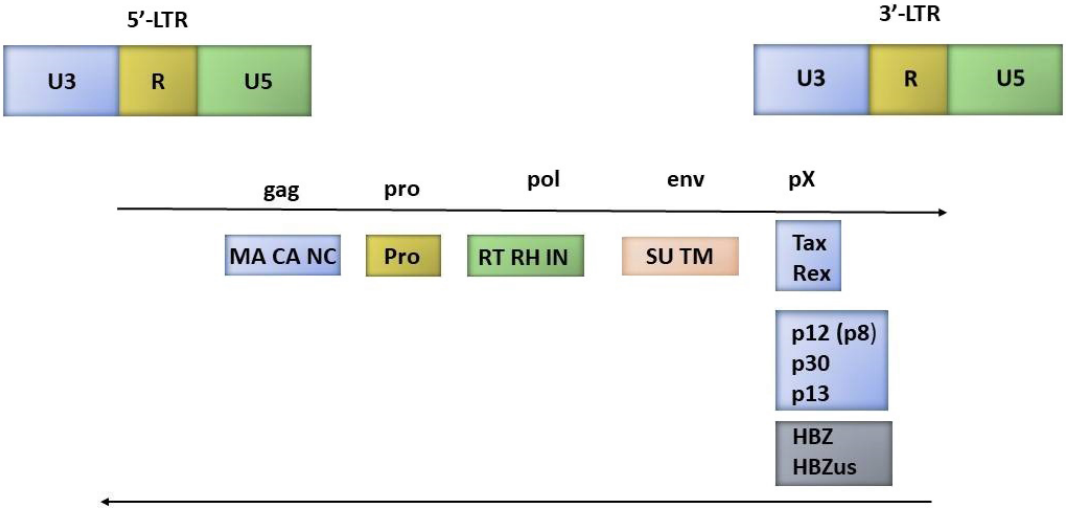

Figure 1 HTLV-1 Genome scheme: Long Terminal Repeat components: Unique 3′ region (U3), Repeated region (R) and Unique 5′region (U5). Two viral sense and antisense strands. Sense strand: *gag* gene encodes Matrix (MA), Capsid (CA) and Nucleocapsid (NC) proteins, *pro* gene encodes Pro protein, *pol* gene encodes Reverse Transcriptase (RT), RNaseH (RH) and Integrase (IN), *env* gene encodes gp46 Surface Unit (SU) and gp21 Transmembrane Unit (TM). Additionally, the pX region, contains the genes of six viral accessory proteins: Tax, Rex, p12, p13/p8, p30 and Basic Zipper Factor (HBZ) protein spliced and unspliced in the antisense strand. Modified from Hoshino H et al. Front Microbiol 2012 [4].

polymerase II [5]. Subsequent posttranscriptional regulation process is essential for splicing and transport of HTLV-1 mRNA. Then, the viral mRNA is exported from the nucleus to the cytoplasm [5]. Viral proteins are translated and transported to the plasma membrane with two copies of genome RNA that at the virus budding site of the plasma membrane form a virus particle. These budding particles are released from the cell surface, undergoing a maturation process by the action of viral proteases (figure 2) [5].

Viral transmission. HTLV-1 transmission occurs mostly through cell-to-cell contact, unlike other retroviruses, which also spread infecting cells in a cell-free form [6]. Few studies have compared cell free infection with cell-to-cell virus transfer. However, all of them suggest that cell free infection is less efficient [7, 8]. Cell-free virus transmission is often inefficient because specific cell barriers prevent the effective spread. In contrast, viral spread by direct cell-to-cell contact is less affected by these barriers [9]. Consistently, HTLV-1 free virions are poorly infectious for most cell types and are hardly detected in the blood plasma [10]. Thus, effective transmission of virions needs living infected cells. The virus is transmitted through three routes: vertical (mostly through breast-feeding), sexual intercourse, and parenteral route [11]. These will be extensively discussed in a following section. All routes require transferring living infected cells to augment viral transmission by increasing the number of infected cells. To achieve this purpose, infected cells need to evade immune surveillance and promote cellular proliferation in the host [11].

Viral entry. Viral entry by the parenteral route occurs directly through an infected cell or a free virion. Nonetheless, efficient transmission through this route needs cell to cell virus transfer. In the case of transmission by breastfeeding and sexual intercourse, initial infection requires crossing the mucosal barrier and then infection of mucosal immune cells directly or via Antigen Presenting Cells (APCs) [11].The virus could cross the mucosal barrier through various mechanisms [11] (figure 3):

1. Transmigration of HTLV-1 infected macrophages: infected macrophages transmigrate through the epithelium during breastfeeding and sexual intercourse.
2. Transcytosis of viral particles: In this process a virion is incorporated into a vesicle and is transferred from the apical to the basal surface of an epithelial cell.
3. Release of newly produced virions from the basal surface of an infected epithelial cell: HTLV-1 infects an epithelial cell and produces new virions that are then released through the basal surface.
4. Bypass of HTLV-1 infected cells through a damaged mucosa: Infected cells can entry in places where mucosa integrity is damaged.

Viral dissemination. After primary infection, HTLV-1 rep-

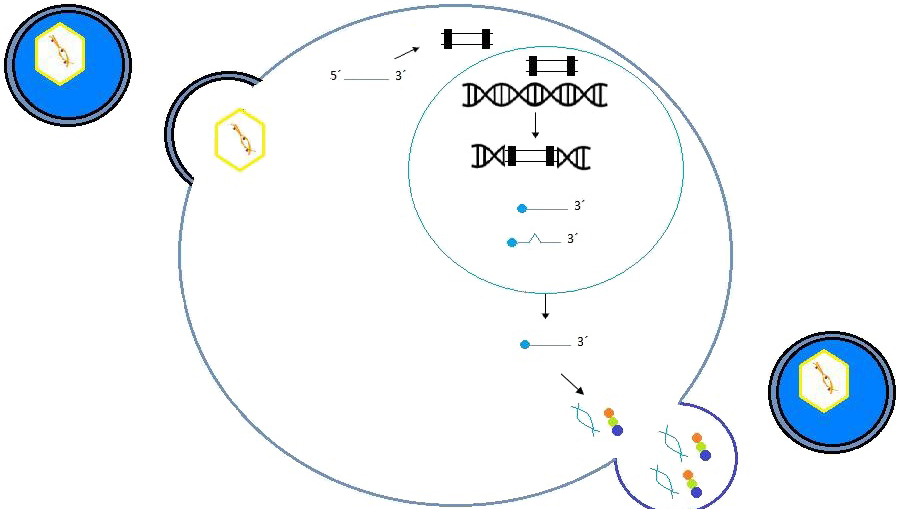

Figure 2 HTLV-1 life cycle: HTLV-1 virion interacts with the target cell surface receptors GLUT1/ HSPG/NRP-1 via the HTLV-1 envelope surface and transmembrane domains of the envelope (Env) protein, then the virion attaches and fuses to the target cell. The viral genomic RNA (gRNA) is delivered into the cytoplasm, undergoes reverse transcription to convert gRNA into double stranded DNA (dsDNA), which is transported to the nucleus and integrated into the host genome. The provirus is transcribed by cellular RNA polymerase II and undergoes post-transcriptional modification (RNA splicing). Spliced and unspliced RNA molecules are exported from the nucleus to the cytoplasm. Viral proteins are translated and transported to the plasma membrane with two copies of gRNA. Viral proteins and gRNA in the budding site form an immature virus particle. Finally, the immature virus particles are released and experiment a maturation process. Modified from Martin J et al. Viruses 2016 [5].

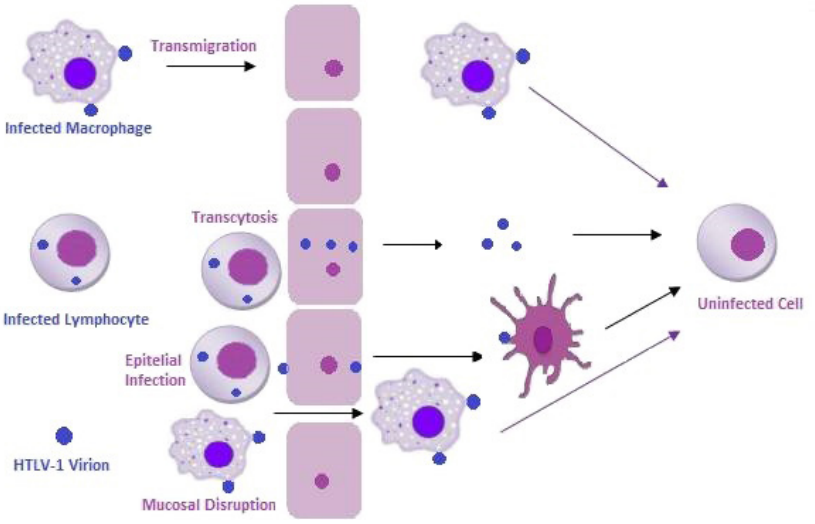

Figure 3 Scheme of possible mechanisms for viral entry: Transmigration of HTLV-1 infected macrophages, transcytosis of viral particles, release of newly produced virions from the basal surface of infected epithelial cells and bypass of HTLV-1 infected cells through a damaged mucosa. Modified from Carpentier A et al. Viruses 2015 [11].

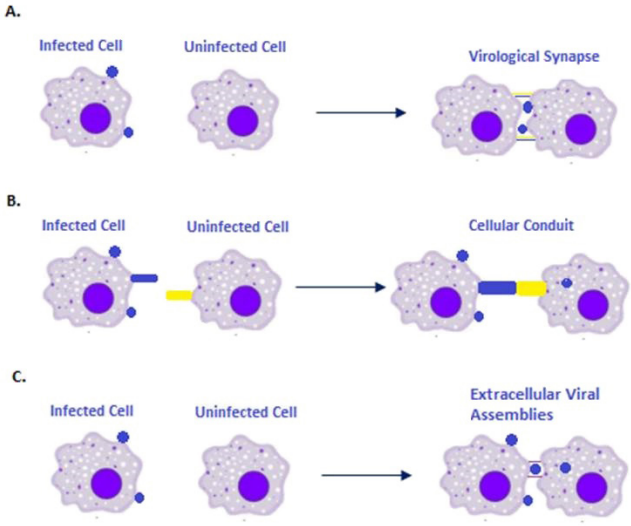

Figure 4 Cell-to-cell transmission of HTLV-1. Scheme of possible mechanisms: A. Virological synapse: An infected cell contacts an uninfected one by interaction between their proteins. B. Cellular conduit: Membrane extensions of an infected or uninfected cell that form cell interactions C. Extracellular viral assemblies: Extracellular viral assemblies adhere to contacting uninfected cells producing HTLV-1 transmission. Modified from Pique C et al. Front Microbiol 2012 [6].

licates by cell to cell transmission and clonal expansion [13]. Cell to cell transmission of virions involves different mechanisms: virological synapse, cellular conduits, and extracellular viral assemblies (figure 4) [12]. The Virological Synapse (VS) is the site of cell to cell contact that promotes viral transmission. It occurs between infected cells and target cells and increases the efficiency of transmission; limiting at the same time the exposure of the virus to the host defense mechanisms [12]. The VS is produced when HTLV-1 infected cell contacts an uninfected cell, by protein interaction between both cells. After this process, the Microtubule Organizing Center (MTOC) is reoriented towards the VS. Then, viral budding is polarized to the VS and newly formed viruses enter the synaptic cleft and interact with cellular receptors. Finally, budded viruses enter the target cell [12].

Another mechanism of cell to cell transmission is by cellular conduits. Conduits are membrane extensions of an infected or uninfected cell. They form interactions among them or with another cell [13, 14]. Cell to cell transmission can also be produced by extracellular viral assemblies when HTLV-1 virions remain attached to the infected cell surface within a matrix formed by virally induced extracellular components. These viral assemblies can be transferred during cell contacts to uninfected cells producing HTLV-1 transmission [14]. Also, HTLV-1 infection is mediated by cell free virions, through interaction of dendritic cells (DCs) with target cells. DCs can store the virus in the surface and transfer the virus to uninfected cells prior to become infected [15].

Viral persistence. HTLV-1 can endure in the organism by two mechanisms in different stages of the infection. The first stage is the acute infection, when cell-to-cell transmission is produced, and the second one, the chronic stage, when virus persists by clonal expansion [16, 17]. In the chronic stage, peripheral blood of HTLV-1 infected individuals contain clones of large number of infected cells with the same integration site [17-20], suggesting that they came from a single infected cell. Furthermore, studies have demonstrated that specific clones can persist over years in an infected individual, suggesting that rather than disseminate from cell to cell, the virus persists in the organism in the long term by mitotic replication of infected cells [21-23].

HTLV-1 HUMAN ROUTES OF TRANSMISSION

As previously said, HTLV-1 can be transmitted through three routes: mother to child transmission, sexual contact, and through HTLV-1 infected blood or cellular blood products.

Mother-to-child transmission. Mother-to-child transmission can be produced through the placenta, perinatally or by breastfeeding [24]. Nonetheless, evidence suggests that transplacental and perinatal transmissions are uncommon [25, 26]. Therefore, most cases of mother to child transmission are produced by ingestion of breast milk. Cell free virions are not usually detected in breast milk, thus transmission by infected cells is much more plausible. In fact, different types of cells that are found breast milk such as lymphocytes, macrophages and epithelial cells of mammary glands can be susceptible to HTLV-1 infection [27-31]. The anatomical site of viral entry is not completely known, but palatine tonsils and gut could be possible options, since their enrichment in potential target cells such as lymphocytes [31]. The mechanism of HTLV-1 crossing through the epithelium is not fully understood. Human enterocytic cells could be susceptible to HTLV-1 infection or via trancytosis mechanism for HTLV-1 virions crossing epithelial barrier and infecting dendritic cells [31].

Sexual transmission. Many questions are still unanswered about sexual transmission of HTLV-1. Few studies are done about the most frequently affected gender. The initial studies suggested that female to male transmission of HTLV-1 was much more frequent than male to female transmission, but later studies have shown that this difference is not as significant as previously thought and male to female transmission could play a more important role [32]. Sexual transmission require entry through a mucosal barrier, the virus could be transmitted through damaged or infected mucosa, or transcytosis across epithelial cells. Consequently, male to female transmission is more efficient in cases of men with history of penile sores or ulcers [32]. However, the semen also contains several cells that could be infected by HTLV-1, such as CD4+ T-cells, macrophages and dendritic cells that can have a role in the sexual transmission [32]. Regarding female to male transmission, in women infected by HTLV-1, infected cells have been frequently detected in cervical inflammatory secretions and cervix carcinoma [33]. In summary, there are very few studies in this field and many questions about mechanisms of sexual transmission of HTLV-1 are still unanswered. Some of the data obtained studying other retroviruses have been extrapolated to HTLV-1. However, not all this information can be faithfully extrapolated to HTLV and therefore, further investigations are needed to achieve more accurate data.

Blood transmission. Blood transmission can occur by transfusion of whole blood or cellular blood products and in the context of needle sharing among intravenous drug users. In the case of blood transmission, passing across a mucosal barrier is not needed, and infected cells can transmit the virus directly by cell to cell transmission or by cell free transmission to dendritic cells. As we saw previously with other routes of transmission, cell to cell transmission is also the most effective way to transmit the virus by blood. A study that compared viral transmission following transfusion of plasma from individuals with different human retroviruses showed that seroconversion occurred in 89% of the individuals who received plasma from HIV-1 infected individuals, but in none of those who received plasma from HTLV-1 or HTLV-2 infected individuals [34]. Of interest is the relationship of transmission with inflammation and malignancy. Several studies suggest that individuals who acquire HTLV-1 by blood are more prone to develop inflammatory disorders, while individuals who acquire the virus during breastfeeding are more likely to develop T cell malignancies [35, 36]. In addition to some factors that can modify this likelihood, such as age of infection, amount of virus and immune response, this implies that the mechanism of infection could affect to different cell populations and it could be a determinant to develop an inflammatory disease or cancer [36].

EPIDEMIOLOGY. HTLV-1 WORLDWIDE DISTRIBUTION

Soon after HTLV-1 was discovered and associated with ATLL, researchers from Japan and America began several studies about distribution and origin or HTLV-1. At early 1980´s was evidenced that Japan was a high endemic area for HTLV-1. However, it was shown that Japan has an uneven distribution

of HTLV-1 carriers, with the greatest prevalence in Southwestern Japan. The cause of this peculiar distribution is still under discussion [37]. Further studies in America and the African continent demonstrated that the Caribbean and many African countries are also HTLV-1 endemics areas [37].

Nowadays, the Southwestern part of Japan, sub-Saharan Africa and South America, the Caribbean area, Australo-Melanesia and foci in Middle East are considered endemic regions of HTLV-1 [37]. Nonetheless, according Gessain and Cassar [37], the world distribution, global and loco-regional estimation of the HTLV-1 prevalence remain yet poorly known because of many factors. On one hand, several regions have not been investigated for HTLV-1 infection, on the other one, the assays used for HTLV-1 serology had some lack of specificity in 1980s-1990s leading to an overestimation of HTLV-1 prevalence. Furthermore, most of the studies were performed in series of blood donors, pregnant women or hospitalized patients. An important point that these authors emphasize is the heterogeneous HTLV-1 distribution. HTLV-1 is present usually in small foci or clusters with high prevalence of infection, nearby areas of low prevalence, as was exemplified in Japan. The cause of this peculiar distribution is not well understood. Gessain and Cassar suggest that it could be due to a founder effect in some groups, followed by the persistence of a high viral transmission rate [37].

HTLV-1 ASSOCIATED DISEASES

HTLV-1 is the causative agent of two clearly related entities: Leukemia-Adult T Cell Lymphoma (ATLL) and Tropical Spastic Paraparesis (TEP). Other inflammatory diseases such as uveitis and dermatitis [38, 39], and infectious diseases such as Strongyloidiasis and Tuberculosis have also been associated [40, 41].

Adult T cell Leukemia-Lymphoma (ATLL). ATLL is a highly aggressive T cell malignancy that affects CD4 + T cells infected by HTLV-1. It has four clinical subtypes: smoldering, chronic, acute, and lymphoma subtypes [42]. This classification is based on diagnostic criteria such as lymphadenopathy, splenomegaly, hepatomegaly, hypercalcemia, organ infiltration and skin involvement. Depending on ATLL subtype, the patients can present numerous signs and symptoms, such as fever, cough, jaundice, ascites, pleural effusion and opportunistic infections [42]. The exact mechanism of ATLL pathogenesis is not fully elucidated, although it is considered a multistep carcinogenesis process in which HTLV-1 infection represent the first step. Several events contribute to the transformation of HTLV-1 infected T cells [43]. ATLL arises as a result of a clonal proliferation of HTLV-1 infected cells, with a progressive malignant transformation. Viral regulatory proteins of HTLV-1, Tax, Rex and HTLV-1 Basic Zipper Protein (HBZ) play important roles in the oncogenic process of ATLL, promoting viral persistence, growth stimulation, and tumor development [43]. Philip S et al performed studies on cultures of HTLV-1 infected HeLa cells. They revealed that a high level of Tax/Rex expression in infected cells overrides HBZ to promote viral replication and cellular senescence. Approximately 98% of HeLa cells infected by HTLV-1 in culture become senescent. However, when the levels of Tax/Rex are low, NF-κB activation and senescence are inhibited by HBZ. Some infected cells undergo mitotic expansion, remaining in latency in asymptomatic carriers. But, other cells, presumably premalignant, continue to evolve, propelled by the acquisition of genetic abnormalities, eventually giving rise to ATLL (figure 5) [43].

Further studies are needed about the process that leads to clonal expansion and progression to malignancy as well as genetic and epigenetic abnormalities that lead to ATLL. ATLL treatment is based on chemotherapy, consisting on CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) or CHOP-like treatments Also Zidovudine and IFN-α are considered and Allogeneic Stem Cell Transplantation following chemotherapy is used in some cases [44].

Tropical Spastic Paraparesis (TSP)/ HTLV-1 Associated Myelopathy (HAM). HTLV-1 produces a central nervous system inflammatory disease known as Tropical Spastic Paraparesis/HTLV-1 Associated Myelopathy (TSP/HAM) [45]. TSP/HAM patients can present neurological signs and symptoms such as weakness of the lower limps, lower back pain, and bowel and bladder dysfunction, as a result of spinal cord lesions and myelin loss. Further studies have reported an accumulation of HTLV-1-specific T lymphocytes within cerebrospinal fluid [45]. These cells can kill HTLV-1 infected cells, but at the same time they release inflammatory cytokines such as IFN-γ that may damage glial cells and neurons [46]. Treatment is focused in treating clinical symptoms with anti-inflammatory therapy. Corticosteroids; IFN-α and IFN-β1 currently represent treatments with limited results. Consequently, more studies are needed in this field [47].

Other HTLV-1 associated diseases. Besides ATLL and TSP/HAM, HTLV-1 infection is associated with inflammatory diseases such as uveitis, conjunctivitis, Sicca syndrome, interstitial keratitis, infective dermatitis, arthritis, myositis, Sjögren's syndrome, Hashimoto's thyroiditis, Graves' disease and polyneuropathies. It is also associated with other infectious diseases such as tuberculosis and strongyloidiasis [48]. Associated opportunistic infections, such as tuberculosis are often developed in ATLL patients, due to their immunocompromised state and associated treatment [48]. Disseminated infection by *Strongyloides stercoralis* in the context of HTLV-1 infection is probably due to decreased secretions of IgE, IL-4, IL-5 and IL-13, which potentiate anti-helmintic response [49]. Thus, HTLV-1 infection is considered a risk factor for *S. stercoralis* dissemination. This parasite infection has been related to HTLV-1 clonal expansion in asymptomatic individuals [49]. Also, HTLV-1 infected individuals with infective dermatitis have an increase of HTLV-1 positive clones. Hence, it could be appropriate to treat *S. stercoralis* and infective dermatitis in HTLV-1-infected individuals, to reduce the risk of clonal expansion [49].

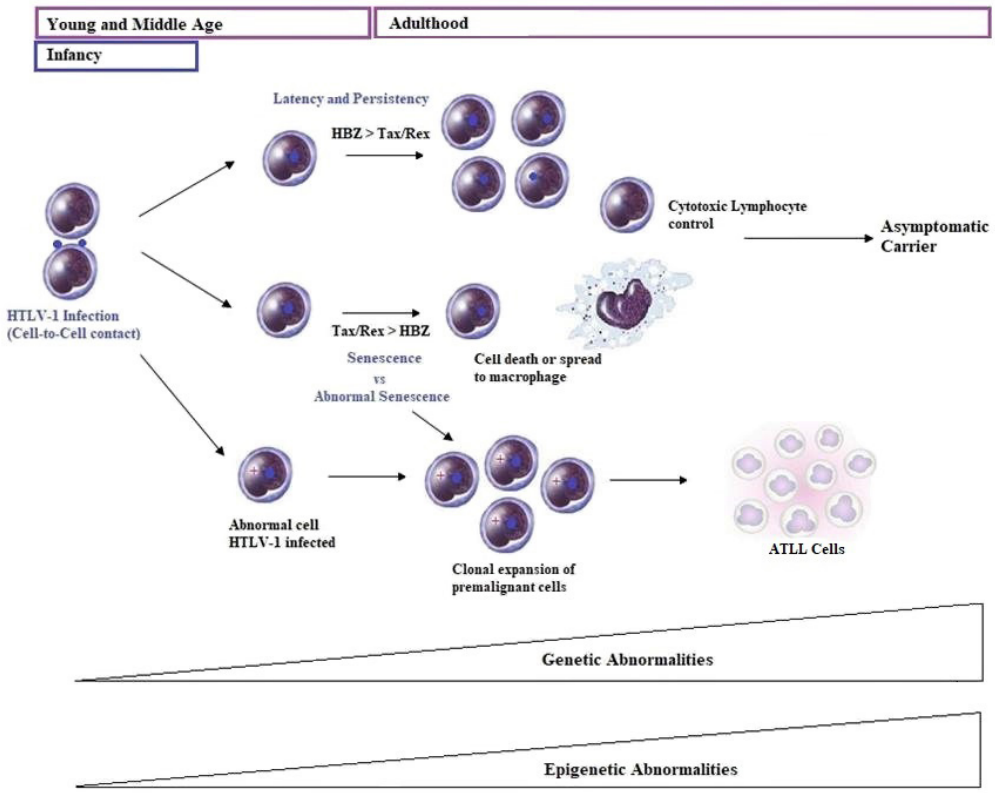

Figure 5 Schematic depiction of HTLV-1 infection (Cell-to-Cell contact) and viral persistence. Infected cells can become latent or drive senescence, depending on HBZ and Tax/Rex expression. When the levels of Tax/Rex are low, NF-κB activation and senescence are inhibited by HBZ and some infected cells undergo mitotic expansion, remaining in latency in asymptomatic carriers. High level of Tax/Rex expression in infected cells overrides HBZ to promote viral replication and cells became senescent, finally dying or being phagocyted. Altered process lead to clonal expansion and progression to malignancy, favored by genetic and epigenetic abnormalities. Based on HeLa cells studies Philip S et al [43].

MICROBIOLOGICAL DIAGNOSIS

The diagnostic methods to study HTLV-1 infection include an initial screening test, such as Enzyme-Linked Immunoabsorbent Assay (ELISA) or Particle Agglutination (PA), and a second confirmatory test: Western Blot (WB) or Innogenetics line immunoassay (INNO-LIA). The qualitative and/or quantitative Polymerase Chain Reaction (PCR) could also be used [50]. Repeatedly reactive samples by screening assays must be checked for the presence of specific antibodies for HTLV 1/2 by confirmatory analysis. Western blot (Wb) is the reference test for confirmation of infection, defining a positive or negative result for antibodies against HTLV-1 [50].

Antibody screening ELISA and WB detect antibodies to HTLV- I, using lysates of HTLV-I as substrate. In WB a serum is judged positive for HTLV-1/2 antibodies if reactivity to both the p24 and rgp21e antigens is present. Polymerase chain reaction (PCR), performed on peripheral blood mononuclear cells (PBMC) DNA can also be used as a confirmatory test; however, it is not generally used because it is expensive, and labor-intensive. In conclusion, antibody tests are the best option for routine diagnostic purposes [51]. Studies performed to evaluate the sensitivity and specificity of ELISA tests have evaluated three ELISA kits (Murex HTLV 1/2, anti-HTLV-1/2 SYM Solution and Gold ELISA HTLV-1/2) showing 100% sensitivity for all of them, but different specificity (92-98.1%-99.5%, respectively) [52].

Despite improvements in the WB assays specificity, indeterminate serological patterns are still a concern for routine screening in blood banks in Europe, America and Africa. Thus, it could be an issue for comparative analyses among epidemiological studies [52]. WB assays use specific recombinant proteins for HTLV-I/II Env glycoproteins incorporated into the WB strips, increasing the sensitivity of the blot, and differentiating between HTLV-1 and HTLV-2. The sensitivity of the WB is 97.1% with a specificity of 97.5% [53].

Another test to confirm HTLV-1 is INNO-LIA. This serological confirmatory assay for HTLV shows results for most of the samples considered indeterminate or positive, but untypeable in WB assays. Few studies have compared WB with INNO LIA

and PCR. Nonetheless, further studies with larger populations are necessary to give definitive conclusions [54].

PREVENTION STRATEGIES

Prevention strategies to avoid this malignancy in endemic countries must be focused on the routes of transmission [55].

Prevention of vertical transmission. As said before, Mother-to-Child Transmission (MTCT) can be produced through the placenta, perinatally or by breastfeeding. However, transplacental and perinatal transmissions are uncommon, and most cases of MTCT are produced by ingestion of breastmilk [56]. Prenatal screening for HTLV-1 should be employed in endemic areas, combined with giving detailed information about HTLV-1, mother-to-child transmission and infant feeding strategies. Recommendations to avoid MTCT include the use of exclusive formula feeding or breastfeeding for a maximum of 3 months, except for high-risk infants, such as premature babies or those living in developing countries with risk of malnutrition. In this cases breastfeeding is justified. Also, it is recommended to test the child for HTLV-1 antibody at three years of age [56].

Blood transmission. Blood transfusion is another possible transmission route and it is considered a major risk for HAM/TSP development [56]. Screening of blood donor is an effective prevention strategy for HTLV-1 transmission. In the case of HTLV-1 non-endemic areas, risk of HTLV-1 infection might be enhanced in some selected donor populations, such as immigrants from endemic areas, with recommendations of policies for selective donor recruitment [56]. For developing countries, the cost of imported screening test kit is high. More cost-effective strategies for blood donor screening need to be developed [56].

Sexual transmission. Recommendations and counseling to prevent sexually transmitted infections include condom use and avoiding multiple and unknown sexual partners. The access to correct information about HTLV-1 infection and appropriate counseling is essential, because blood donor candidates and sexually active people are usually asymptomatic [56].

HTLV-1 SCREENING IN SELECTED POPULATIONS

Transplant donors. HTLV-1 screening should be done in all transplant donors with risk factors (immigrants who were born or lived in endemic areas, travelers to these endemic areas and family of these immigrants or travelers) or when the organ is going to be transplanted in countries where determination is mandatory [57-59]. Spain is a leader in the world of transplantation with a donation rate of 46 donations per million inhabitants. 8% of these donors are resident immigrants, and more than 20% of this population comes from endemic countries for HTLV-1 [60, 61].

Since 1990 and to date, about 20 cases of TSP have been reported in Spain, who have developed myelopathy in less than 2 years, and others like ATLL [62-66]. Pre-transplant screening, a protocol, which has been regulated since 2012 and reviewed in 2014 (BOE, November 5th, pp. 90536-8) for donors from endemic areas, relatives, and those with history of sexual intercourse with them, is important in this regard [64]. However, due to the current importance of migratory flows from endemic areas to HTLV and their characteristic transmission mechanisms, it is very difficult to screen for risk factors [64]. Therefore, it is advisable to determine specific antibodies against HTLV 1/2 in all organ donors.

Other immunosuppressed patients. HTLV-1 is associated with a higher incidence of opportunistic infections [67]. In endemic countries, physicians must consider the patients current HTLV-1 infection status in immunosuppressed patients, because it is believed that opportunistic infections in HTLV-1 positive patients are not caused by the virus itself, but by alterations in the host immune system [67]. Treatment of HTLV-1 is difficult due to the lack of effective antiretroviral agents [67]. Therefore, we must consider HTLV-1 screening and prophylaxis strategies in the case of immunosuppressed patients (patients on chemotherapy or biological therapy).

TREATMENT

Antiviral/ antibiotic therapy. No effective treatment for HTLV-1 has been described so far [68]. The effect of Zidovudine plus Lamivudine was analyzed in four HTLV infected patients, two of them with TSP/HAM and coinfected with HIV. There was a virological and clinical improvement and an increase and posterior decrease of HTLV-1 proviral load [68].

Moreover, many ATLL patients were efficiently treated with a combination of zidovudine and interferon α (AZT/IFN-α), with arsenic trioxide added in some cases [68]. Nonetheless, *in vivo* reverse transcriptase (RT) activity is low, which suggest a clonal mode of viral replication that leads infected cells to become resistant to AZT. Moreover, histone deacetylase inhibitors (HDACi) associated to AZT prevent de novo cellular infection and in asymptomatic STLV-1 infected non-human primates, HDACi/AZT produces a strong decrease in the proviral load, although unfortunately there is a posterior rebound effect [68]. Also, the antiviral effect of raltegravir on HTLV-1 carriers was analyzed in a pilot and open study carried out on five individuals, showing that this treatment does not result in a significant reduction of proviral load beyond 6 months of therapy [69].

Furthermore, a prospective study of effect of transient antibiotic treatment on tumor cells showed that transient aggressive antibiotic therapy was associated with decreased expression of IL-2 high-affinity receptors (CD25), STAT3 signaling, cell proliferation in lesional skin and clinical improvement. This provides evidence on aggressive antibiotic treatment inhibiting malignant T cells in lesional skin, which could be useful for future ATLL therapies [70]. However, further investigations are needed in this field.

HTLV-1 Vaccine. HTLV-1 vaccines have been studied

since late 80's to early 90´s [71]. These were partially effective [71-74]. The Franchini group (NCI) proved a vaccine to immunize New Zealand white rabbits, with the entire envelope protein of the HTLV-1 obtained from the DNA of a West African healthy HTLV-I-infected patient [74]. This showed initial protection against the virus, but finally a combination protocol failed, which suggest that administration of this preparation might be ineffective [73]. Nonetheless, recent studies use HBZ as a target in mice, showing an anti-lymphoma effect of the cytotoxic T lymphocytes targeting HBZ, suggesting that this could be more effective than conventional strategies [74]. Furthermore, Sugata et al demonstrated that HBZ could be a target for immunotherapy of ATLL patients. They generated a recombinant vaccinia virus expressing HBZ, which induced specific T-cell responses in mice and macaques. This could be a candidate peptide for vaccine development [75-77]. Despite further investigations are needed, research in this field is severely hindered by the lack of funding for clinical trials.

HTLV-1 AS EMERGENT INFECTIOUS DISEASE IN SPAIN

According to numerous epidemiological studies performed in Europe, mainly in blood donors and in pregnant women, most individuals infected by HTLV-1 living this continent originate in high endemic areas -mostly the West Indies and Africa- or are descendants from natives to these areas [78-96].

Spain is not considered an endemic country for HTLV-1; although the incidence of cases has increased since 2008, when screening was introduced in blood banks and there was an increase of immigration and tourism from endemic regions [97]. In Spain, most of the HTLV-1 infected individuals are from Latin America [97, 98]. In recent years, the number of new cases diagnosed in Spain has been stable, around 20-25 cases every year [98].

There are also cases of HTLV-1 infection in Spain among patients who have received an organ transplant; specifically, 2 patients were reported in the HTLV-1 Spanish Registry [98] with liver and renal transplant from the same HTLV-1 infected donor, who developed TSP in a period of 2 years, due to the induced immunosuppression [98].

National studies on the prevalence of HTLV-1 infection in Spain indicate that it is stable and low. The virus is not prevalent in Spain and a total of 327 registered cases until December 2016 were reported, 62% in Latin American immigrants and 13% in African immigrants, with less than 20% Spanish native cases. Between 20 and 25 new cases are diagnosed every year, however, their incidence is likely to be higher, since migratory movements from endemic areas and racial mixing enhance their acquisition and transmission. Therefore, it is likely to remain underdiagnosed [98]. Throughout life, approximately 10% of these patients infected with HTLV will develop an HTLV-1 associated disease. Thus, it is necessary to be expectant, given the high emigration rate of endemic regions, especially from Latin America [99].

CONCLUSIONS

HTLV- infections is considered a neglected disease nowadays, despite infecting at least 10 million people worldwide. Spain is not an endemic region for HTLV-1, but it receives a large influx migration from highly endemic regions, mainly from Latin America, thus it could be a region with emerging risk of HTLV-1 infection. So, it is important to be expectant of HTLV-1 Spanish Registry, to develop preventive strategies in vulnerable groups. Viral screening is justified in transplant donors as well as in blood donors. Specificity in confirmatory test is an actual issue that require further investigations. Furthermore, research to avoid infection and associated diseases focused on the development of effective treatments or vaccine against the virus is needed.

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