IMPACT OF HUMAN T-LYMPHOTROPIC VIRUS TYPE 1 (HTLV-1) INFECTION IN THE PUBLIC HEALTH CONTEXT IN BRAZIL

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ABSTRACT

Human T-lymphotropic virus type 1 (HTLV-1) is a retrovirus associated with diseases with broad clinical conditions. HTLV-1 infection is not curable, it is asymptomatic in most carriers, and its diagnosis is rarely made early. Brazil has a large number of operators, however, it does not have effective programs to contain the transmission of the virus. Few studies on the subject are done in depth, which contributes to the poor delay in the progression of degenerations associated with HTLV-1. The lack of information, even from health professionals, makes therapy even more difficult. The study aims to recognize the importance of HTLV-1 infection in the context of Public Health in Brazil through a research of an observational nature, with a descriptive approach, technical procedures for bibliographical and narrative review, with a cross-section on the development of Time. We analyzed and extracted information on pathogenesis, epidemiology, forms of transmission, risk factors, diagnosis, treatment, infection prevention and HTLV-1 associated diseases.

KEYWORDS: HTLV-1, HTLV-1 infections, Human T-Lymphotropic Virus 1.

1. INTRODUCTION

Retroviruses are important causes of human morbidity and mortality and have caused pandemics in recent decades. Among them, Human T-lymphotropic Virus Type 1 (HTLV-1) have long-term, silent persistence in the host, remaining for several years. It is estimated that at least 20 million people are infected worldwide[1,2,3], and Brazil has about two million people infected with the virus, accounting for up to 2% of the infection in blood bank samples in some regions of the country[3,4].

Since its description, HTLV-1 has been associated with a range of diseases, such as tropical spastic paraparesis/ HTLV-associated myelopathy (HAM/ TSP), Adult T-Cell Leukemia/ Lymphoma (ATLL), and uveitis associated with HTLV (HAU). Although in most cases carriers remain asymptomatic, 2-6% of infected individuals develop ATLL[5,6] and another 2-3% develop HAM/ TSP[7,8]. Descriptions also occurred of HTLV-1 associated with uveitis[9,10], dermatitis[11], alveolitis/ bronchiectasis[12], arthritis[13], nephritis[14] and myositis[15], but there is little data on prevalence[16].

The chance of transmission of the virus is characterized by the dependence of the efficiency of the transmission route, the infectivity of the donor, the susceptibility of the receptor and the number of exposures. The risk of transmission is higher with non-depleted leukocytes in blood transfusions (8.6-64%)[17], The chance of transmission of the virus is characterized by the dependence of the efficiency of the transmission route, the infectivity of the donor, the susceptibility of the receptor and the number of exposures. The risk of transmission is higher with non-depleted leukocytes in blood transfusions (8.6-64%), presuming to be high in organ transplantation, needle and syringe sharing based on anecdotal reports, even less with transplacental exposure (~ 3-5% of all infected mothers) breastfeeding (up to 22% if breastfed for 18 months) and unprotected sex (~ 1% a year between stable, discordant partners)[18,19,20,21,22]. In endemic areas, transmission has peaks at two time points[23]: in early life through breastfeeding and after childhood through unprotected sex[24], with some suggestion of increased risk of infection in postmenopausal women. Seropositivity has been associated with advanced ages [23], female[25], number of lifetime sexual partners[23], commercial sex work[26] and history of genital ulcers[27].

The misinformation and difficulties faced by HTLV-1 carriers during the diagnosis and treatment phase reflect the neglect of transmission containment, dissemination policies on the virus and its associated diseases and the encouragement of research, central public health agencies[28].

In Brazil, this is justified by the deficient screening of the virus, a reduced number of sites / centers that carry out the diagnosis at a satisfactory laboratory level, and especially, the follow-up of the patients carried out by a few specific health care centers targeted for this purpose. In a booklet made available by the Federal Government, through the Ministry of Health, the body recognizes the problem by exposing the non-existence of a proposal for HTLV-1 screening in primary care for Sexually Transmissible Infections (STIs) due to restrictions on access to diagnosis and treatment[29]. In the country, only blood donors make

compulsory screening tests, which makes it difficult to identify, treat and contain the transmission[30].

In addition, the list of notifiable diseases in Brazil does not include HTLV-1 infection, which causes serious restrictions in identifying the prevalence and incidence of the virus/ disease in the country[31].

Currently, due to the "negligence" of this infection, it is rare that the patients receive advice and preventive guidance regarding its transmission. Thus, the counseling work for people living with this virus is fundamental and requires multiprofessional assistance able to deal with the subject.

This study aims to recognize the impact of HTLV-1 infection in the context of Public Health in Brazil, to present the fundamental aspects concerning the virus and to propose a better understanding of this silent infection, which is so little known, both by virus carriers and professionals of the health area.

2. MATERIAL AND METHODS

This research is based on a study of observational nature, with a descriptive approach, technical procedures of bibliographical research, narrative revision and transversal cut as to the development of time.

The literature was updated using the following databases: LILACS (Latin American and Caribbean Literature in Health Sciences), PUBMED (National Library of Medicine / National Institutes of Health) and SCIELO (Scientific Electronic Library Online). As search criteria we used the keywords: *"HTLV-1 Infections"; "HTLV-2 Infections"; "Human T-lymphotropic virus 1"; "Human T-lymphotropic virus 2" "Nervous System Diseases"; "Paraparesis Tropical Spastic"; "Neuromuscular Diseases"; "Strongyloidiases"; "Dermatitis"; "Skin Deseases" e "Leukemia-Lymphoma, Adult T-Cell"* and their correspondents in Portuguese. In order to delimit the search, the limits were used: human; publications written in Portuguese or English; available in full; with free electronic access; period from January 1997 to September 2017. Based on the titles and abstracts generated by the search, we selected the studies that approached the subject of the review. References of selected articles were used to access other publications, when considered important for clarification of the subject. Exclusively unavailable letters, reviews, editorials and publications for online access were excluded.

3. LITERATURE REVIEW

The virus

HTLV-1 is classified in the genus *Deltaretrovirus* of the subfamily *Orthoretrovirinae* of retrovirus[32]. It was the first human retrovirus described, initially associated with Adult T-cell Leukemia (ATLL) in Japan in 1977, and was later found in several parts of the world. It was isolated in 1980 from a patient with cutaneous T-cell lymphoma[33]. Subsequently, it was also associated with inflammatory diseases, such as HAM / TSP and HAU.

HTLV-2 (Human T Lymphotropic Virus Type 2 T-Lymphotropic Virus) was identified in 1982 in a continuous line of T cells obtained from a patient with tricholeukemia (hairy cell leukemia), and presented antigenic differences compared to HTLV-1[34]. It is not often associated with neurological cases[4], however, Gabet *et al.* (2006)[35] described the appearance of lymphomas in patients with this virus.

The nucleotide sequences of HTLV-1 and HTLV-2 show a similarity of 65%. The genetic variability observed between samples of both HTLV-1 and HTLV-2 has led to the description of subtypes and phylogenetic analyzes show the evolutionary relationships between them. HTLV-1 is classified into four subtypes (A-D). The subtype A (cosmopolitan) is the most widespread, being found in many populations and geographical areas and comprises four molecular groups, the Japanese, the transcontinental and of North Africa and the East. There is no relation between the subtype and the disease caused by the virus sample, with the genomic variability of HTLV-1 being much more dependent on its geographical origin[36].

In 2005, two new types of HTLV - HTLV-3 and HTLV-4 were described in populations of southern Cameroon that have contacts with non-human primates[37,38]. The origin of HTLV-3 appears to be STLV-3, but for HTLV-4 no equivalent of STLV has been identified, and it is also phylogenetically distinct from known HTLVs. It is not yet known whether HTLV-3 and 4 can be transmitted between humans and whether they are capable of triggering diseases in their carriers, as with other HTLVs[38,39].

Similar to HIV-1 in a distance relationship, HTLV-1 is a complex retrovirus because, in addition to the gag, pol and env genes being controlled by other competent replication exogenous retroviruses, HTLV-1 encodes several genes whose products regulate transcription viral replication and propagation[40,41,42]. The most important of these regulatory genes are *tax* and HBZ [43,44]. The *tax* gene transforms the transcription of the virus itself, providing a strong positive feedback loop. In addition, it transforms many host genes, namely those encoding the α-chain of the IL-2 receptor (CD25), interferon-γ and the intercellular adhesion molecule 1 (ICAM1). As a consequence, tax exerts a remarkable role in the infected cell, including activation, proliferation, inhibition of cycle control points and inhibition of cell DNA repair[41,42,44]. HBZ acts at both the RNA and protein levels to promote proliferation of the infected cell[45] and oppose many of the *tax* actions[43].

It is an enveloped virus, with a diameter of approximately 100 to 140 nanometers (nm), having in its core about 80 to 100 nm. This retrovirus is characterized by presenting two protease molecules, together with a genome composed of two single strands of RNA with positive polarity, each of which is

accompanied by a molecule of the enzyme reverse transcriptase[46].

The viral core consists of the following structural proteins: nucleocapsid (p15), capsid (p24) and matrix (p19). In the envelope are the transmembrane glycoproteins (gp21) and surface glycoproteins (gp46), which present a difference in the pattern of bands to the electrophoresis, which allows to point out types 1 and 2 of HTLV[47].

HTLV-1 integrates a single copy of provirus DNA into each cell that infects[48]; it is not known what prevents a second copy from becoming integrated. The genomic location of the provirus is identical in each cell of a clone, but differs between these[49].

The presence of the virus in the individual does not necessarily cause health problems. Different factors in the virus/ host/ environment interaction collaborate in the development of a disease, which may be a hematological manifestation (leukemia/ T-cell lymphoma), inflammatory (myelopathy, uveitis, rheumatoid arthritis, etc.) or diseases with parasitic agents, such as hyperinfection by Strongyloides stercoralis. The CD8+ T cell response (*cluster of differentiation* 8+) is the event that determines the course of the infection[50].

HTLV-1 can infect most types of nucleated cells in vitro, but in vivo about 95% of the proviral charge is located on CD4+ T cells, followed by CD8+ T cells and, rarely, dendritic cells. It spreads by cell-cell contact, with ICAM1 involvement in the cell infected with lymphocyte function-associated antigen 1 (LFA-1, also known as α-L integrin) in the "target" cell triggers the onset of the virus to the area of cellular contact in a specialized structure with microdomains of organized proteins denominated virological synapse[51].

Epidemiology

HTLV has infected human populations for thousands of years, with a worldwide distribution. However, most studies related to virus prevalence are based on distinct population groups such as pregnant women, blood donors, haematological patients and injecting drug users, which does not represent a significant sample of the general population[3].

Despite this, it is estimated that HTLV-1 infection represents a global epidemic. The prevalence varies according to the geographical area studied, the socio-demographic composition of the population and individual risk behaviors. These factors determine a spatial variation of prevalence rates within each specific area[3].

The main endemic areas of infection include Africa, South and Central America, the Caribbean, Japan, Melanesia, and the Middle East. In South and Central America, Argentina, Bolivia, Brazil, Chile, Colombia, Honduras, Panama, Peru and Venezuela stand out[4].

There are two hypotheses proposed to explain the origin of this retrovirus in the American continent. One is the prehistoric human migration of infected populations across the Bering Strait, where they brought the virus from northeast Asia to the region, the other suggests that Africans and Japanese introduced the virus on the continent with the arrival of black slaves and later of Japanese immigrants[52].

According to Catalan-Soares *et al.* (2005)[53], a serological survey for HTLV-1 and HTLV-2 among blood donors was carried out between 1995 and 2000, now in 26 Brazilian capitals and in the Federal District. The results showed a great heterogeneity among the capitals, with prevalences varying from 0.4/ 1000 in Florianópolis, located in the southern region of the country, to 10.0/ 1000 in São Luís, in the northeast region.

In Brazil, infection has the world-wide pattern of epidemiological characteristics: seropositivity increases with age, being higher in individuals at risk behavior to acquire sexually transmitted diseases, in poly-transfused patients and in intravenous drug users[54].

In the Amazon region, the high prevalence of HTLV infection has been highlighted in the national scenario, with Pará being the third state in the number of cases among 7.8 blood donors in Brazil[53,55], which has led to seroepidemiological and molecular studies directed to communities with specific populations. There are records of the prevalence of 1.8% for HTLV-1 among 20 Japanese immigrants living in the municipality of Tomé-Açú (PA)[56], variation from zero to 2.06% in remaining communities of quilombolas, in the Island of Marajó-PA[57] and in a rural population-based study conducted in easily accessible riverside communities in Belém, a prevalence of HTLV-1 was found for 1.14%[58]. HTLV-2 has also been identified in up to 30% of 22 Amazonian indigenous communities[59].

A didactic classification offered by the Brazilian Ministry of Health indicates that regions with more than 5% seropositivity are considered high prevalence, between 5% and 1% of average prevalence and less than 1% of low prevalence for HTLV-1[54].

Forms of infection transmission

HTLV can be transmitted in two ways: horizontal (sexual contact, blood transfusion and the use of contaminated needles and/ or syringes), with the most efficient sexual transmission from man to woman. It is estimated that this efficiency is about 60%, being 4% in the opposite direction[60,61]; and vertical (maternal-infant transmission), mainly through breastfeeding. For transmission to occur, there is a need for the presence of infected cells[60,62,63].

According to Gessain & Cassar (2012)[3], vertical transmission may be intrauterine (transplacental) communication, perinatal (direct contact with blood), and, mainly, through breastfeeding. Breastfeeding is responsible for a prevalence of up to 25% transmission of infection in children born to HIV-positive mothers.

However, transmission of HTLV by blood transfusion seems to be the most effective means. It can happen with the transfusion of cellular products of the blood (whole blood, red cells and platelets), but not with the fraction of plasma or derivatives[48,64]. Studies

in Japan[18], Jamaica[19] and the United States65 demonstrated that transfusion transmission factors included storage of blood product for less than one week, male sex, and immunosuppression at the transfusion receptor. Other studies have also shown that plasma and its derivatives (albumin, immunoglobulins, antihemophilic factors) do not transmit HTLV[66,67].

Infection is considered lifelong and most infected individuals remain asymptomatic, becoming viral reservoirs and continuing the chain of transmission[68]. The efficiency of the dissemination of HTLV-1 is related to the transmission route[69]. Although the main risk of infection in developed countries appears to be the use of needles contaminated by drug users in developing countries, such as Brazil, transmission is mainly intrafamiliar[68,70,71,72,73].

Risk Factors for Infection

Studies show that unprotected sex, multiple sexual partners, presence of genital ulceration and paid sex increase the risk of HLTV transmission[63,74,75]. In addition, prolonged breastfeeding is also recorded as an important route of transmission of the virus[76,77,78].

As a parenteral route, the sharing of needles and syringes among injecting drug users (IDUs) is another important route of HTLV-1 transmission in developed countries[79,80], in addition to transfusion by contaminated blood cell components[19,81].

It is worth remembering that blood transfusion was also a significant risk factor for the transmission of HTLV-1 before 1994, when screening for HTLV was not yet mandatory in Brazilian blood banks. In a study conducted in Salvador, state of Bahia, it was observed that HTLV-1 positive women received more blood transfusion than seronegative women before 1993[82].

In this study carried out in the city of Salvador (BA), the behavioral characteristics were also verified through the comparison between the HTLV-1 infected and the seronegative women. The age of the first sexual intercourse, number of sexual partners in the life, presence of STIs and blood transfusion were the variables that presented significant difference between the groups evaluated. In the comparison between the seropositive and seronegative groups, anal sex practices were also associated with HTLV-1 seropositivity, whereas the presence of STIs did not remain significant[82].

Several studies have reported that indicators of more vulnerable socioeconomic status, such as formal education, are associated with increased prevalence rates for HTLV-1 in endemic and non-endemic areas[19,83,84,85,86]. These data suggest that social and environmental factors associated with poverty can influence the transmission of HTLV-1 in both endemic and non-endemic countries. And it is precisely those countries endemic to HTLV-1 (with the exception of Japan), generally with worse indicators of socioeconomic status and human development, which deal with the higher burden of diseases associated with HTLV-1.

Diagnosis

The serological diagnosis of the infection is based on the detection of specific antibodies against the virus. Because retroviruses integrate into the host genome and remain in the infected cell until their death, a retrovirus infection is lifelong, however, the virus may remain in the individual with a low replication. Serological methods for diagnosis of HTLV infection can be classified into two categories: screening and confirmatory tests[87].

At the outset, a plasma/ serum antibody test is performed by means of a low-cost screening test, the enzyme-linked immunosorbent assay. Because they have low specificity, these tests often show false positive results. It is therefore recommended to confirm by indirect immunofluorescence or *Western Blot*. These tests aid in the distinction between HTLV-1 and HTLV-2, but may present undetermined results, which makes it imperative to perform PCR (polymerase chain reaction) for diagnostic confirmation because of its high sensitivity. Undetermined negative PCR results may indicate exposure to the virus and are indicated for follow-up[88]. Atypical lymphocytes (Flower Cells) can be observed in peripheral blood, as well as hypergammaglobulinemia and false-positive results for syphilis[89].

Recently a new PCR technique was developed called real-time PCR. Through luminescent probes or using dyes that bind to the double strand of DNA it is possible to detect the PCR product during its synthesis in the apparatus itself where the amplification reaction is taking place. This technology, besides detecting, can also quantify the number of copies present in the sample[90].

One variation of this technique is quantitative real-time multiplex PCR, in which two or more target sequences can be amplified, including more than one pair of primers in the same tube. HTLV-1 and HTLV-2 in the same reaction, has the advantage of using a technology that reduces the possibility of cross-contamination and allows the amplification of several samples in the same run, without step post-amplification, thus decreasing the time spent and providing good results[91].

PCR has become the reference method for determining the status of infection and distinguishing HTLV-1 from HTLV-2. It is valuable in the characterization of samples not typed by serology and in the resolution of indeterminate cases in *Western Blot* tests. PCR is also useful in the early diagnosis of mother-to-child transmission in children up to two years of age, since serological tests can not be indicative of infection because of passive transfer of maternal antibodies. PCR is also used to detect infection in the period between exposure and seroconversion[87].

There is as yet no formal indication for quantitative testing, but studies suggest a high proviral load ratio

with progression of HTLV-1 associated diseases[19,91,92,93].

Diseases associated with the virus

Most individuals with HTLV-1 remain symptom-free for years, although there is a possible relationship of immunosuppressive, neoplastic and inflammatory effects associated with the retrovirus. Three clinical syndromes have been identified with direct association: Adult T-Cell Leukemia/ Lymphoma (ATLL), HTLV-1 Associated Tropical Spastic Paraparesis (HAM/ TSP)[95,96] and HTLV-1 Uveitis associated to (HAU)[97,98].

Leukemia / Adult T-Cell Lymphoma – ATLL

HTLV-1 is the agent responsible for adult T-cell leukemia/ lymphoma. The probability of developing this disease in the infected is 4%. In Japan, this occurs in 6% of men and 2% of women. The latency time of the infection at the onset of ATLL is long, reaching 60 years in Japan and 40 years in Jamaica[99].

In a systematic review, Oliveira *et al.* (2017)[100] describe, in order of frequency and per country, reported cases of ATLL in Central and South America: 286 (1.8%) cases in Brazil, 183 (2%), in Martinique, 173 (6.1%) in Jamaica, 118 (1.3-3.8%) in Peru, 42 (0.7-1.9%) in Chile, 45 (2.8-5.3 in Trinidad and Tobago, 15 (0.03-0.16%) in Argentina, 6 (%) in Colombia, 23 (4%) in Barbados, 19 (4.4%) in French Guiana, 17 2.6%) in Dominica, 5 (0.037%) in Cuba, 4 in Panama (0.2-2%) and 4 (0.2%) in Venezuela. In another international study of peripheral T-cell non-Hodgkin lymphomas[101], including the United States and European non-endemic countries for HTLV-1 and Asia, serology for HTLV-1 was added for the assessed cases. As expected, they diagnosed ATL in 25% of cases in Asia, 2% in the USA and 1% in Europe.

Diagnostic limitations to differentiate from other diseases in less developed countries suggest an underestimated occurrence of ATLL in the world. An incidence of less than 5% in the endemic areas of HTLV-1[69].

Four clinical forms of ATLL have been described: leukemic, lymphomatous, chronic and *smoldering*. The first two forms are acute and usually invasive and lethal, with an average survival of six to ten months after diagnosis[103]. The acute leukemic clinical form is characterized by atypical lymphocytosis and hypercalcemia, whereas lymphomatosis is like other non-Hodgkin's lymphomas, except for the presence of hypercalcemia and skin lesions. The chronic form and the smoldering present an average survival of 24 months and 42 months, respectively. The smoldering form is a phase between the asymptomatic carrier and the one with monoclonality. It is characterized by less than 4,000 lymphocytes/ mm^3, abnormal mature T-lymphocytes above 5%, persistent skin lesions with treatment and with possible evolution after about 10 years for acute or chronic forms[55]. The latter form usually has a T-lymphocyte count above 3.500/ mm^3, skin lesions and opportunistic infections such as *Pneumocystis carinii*, persistent infestation by *Strongyloides stercoralis* and chronic crusted scabies[19].

It is emphasized that the acute stage may be the evolution of both chronic form and smoldering. Regardless of the initial clinical picture, high rates of serum lactate and calcium dehydrogenase, multiple lesions and age above 40 years are factors associated with a shorter survival time[55].

Appropriate treatment has not yet been established. Chemotherapy used for non-Hodgkin's lymphomas is not effective. Combinations of interferon-α and zidovudine and anti-CD25 antibodies have been tested with good results, but additional randomized studies are still required for these therapeutic options to be definitively consolidated[94,103,104,105,106]. This lack of adequate therapy to improve the prognosis of the disease makes it even more important to prevent the transmission of HTLV-1.

Tropical Spastic Paraparesis/ HTLV-1 Associated Myelopathy - HAM/ TSP

HAM/ TSP is a disorder of slow, chronic and progressive evolution, whose development of neurological manifestations occurs during the first or second year of the disease, due to a reactivation of HTLV-1 infection after a long period of latency and incubation[107]. Clinical progression is faster in middle-aged women in the premenopausal period and in patients with high proviral load, which facilitates HTLV-1 migration by infected lymphocytes to the Central Nervous System (CNS)[108,109].

In fact, because it is a chronic progressive myelopathy, its clinical progression is usually subtle, which makes it difficult to evaluate the progression of the disease, even over a year. Therefore, information on the quantification of biomarkers associated with the severity of the disease, as well as its prognosis, is important to evaluate the effect of the treatment, as well as conducting clinical trials of new therapies[110].

Its neurological status is variable and therefore the most appropriate is to denominate it neurological complex associated with HTLV-1[111]. Atrophy occurs in the lower part of the thoracic medulla94 and through an optical microscopy an inflammatory process is observed as a result of a lymphocytic infiltration with posterior white matter degeneration and a glio-mensenchymal reaction[55]. The study of cerebrospinal fluid (CSF) shows moderate pleocytosis with a predominance of slightly increased or normal lymphocytes and proteins [94].

The mechanism by which HTLV-1 causes neurological damage is still unclear. The possible autoimmune reactions of infected lymphocytes that infiltrate the CNS, due to the mimicry between the viral proteins and the target cells, as well as damage to the endothelial cells (by direct action of the virus and by the action of cytokines produced, such as TNF-α and interleukin-15)[112,113]. As a rule, proviral load and anti-HTLV-1 serum antibody titers are higher in patients who develop a neurological condition

compared to asymptomatic carriers and those with ATLL[94]. Corticosteroids, interferon-α, plasmapheresis, high doses of vitamin C, heparin, azathioprine and anti-IL-2 antibodies have been used as therapeutic options[94,98].

Currently, the World Health Organization (WHO) recommendation for the clinical diagnosis of this disease is based on clinical characterization and demonstration of anti-HTLV-1 antibodies in serum and CSF or proviral load as biomarkers for disease stage classification, although these are not exactly specific for HAM/ TSP[114].

A novel, minimally invasive diagnostic model for early-stage HAM/ TSP detection is being studied through the quantitative differentiation of biomarkers of an entire CSF proteome. Two of them, the cysteine-rich acid secreted protein (SPARC) and the vascular cell adhesion molecule-1 (VCAM-1), were highlighted as useful for the diagnosis of early degrees of HAM/ TSP severity, which could lead to adequate management of the disease before presenting more severe symptoms[114].

Host genetic factors also influence the immune response and pathogenesis of HAM/ TSP. HLA-A * 02 and HLA-Cw * 8 alleles are associated with a protective effect against HAM/ TSP, unlike HLA-DRB1 * 0101 and HLA-B * 5401 are high-risk for the disease. Initial evidence of these effects was made in Japan and later in other countries[115,116]. A study in Brazil confirmed that HLA-A * 02 has the protective effect because it is involved in the reduction of proviral load[117].

Uveitis associated to HTLV-1 – HAU

It is an inflammatory disease of the uvea with a varied etiology, being infectious (tuberculosis, syphilis, cytomegaly, etc.) and non-infectious (sarcoidosis, Behcet's disease, Vogt-koyanagi-Harada syndrome, etc.). However, in approximately 40% of cases the cause is not established. In a study demonstrated by Mochizuki and colleagues (1992a)[118], 35% of the patients submitted to the study with idiopathic uveitis had positive HTLV-1 serology and only in 10% of the cases with a determined etiology.

Its pathophysiology is not defined. The presence of pro-viral DNA in T lymphocytes (most cells in the aqueous humor) is believed to cause the release of cytokines (especially interleukin-6) and leads to the inflammatory reaction[98], suggesting that autoimmune reactions are the cause of damage, as well as the direct action of the virus itself.

There is discreet visual blurring in the clinical picture, of acute or subacute onset and usually unilateral flying flies[10,118]. At physical examination, vitreous opacification, iritis and discreet retinal vasculitis[98]. The diagnosis is suspect after exclusion of the other causes of uveitis in individuals with positive virus serology[119]. It should be noted that the identification of HTLV-1 by means of amplification (polymerase chain reaction or PCR) techniques in monoclonal cells of the vitreous humor can also be performed[94,118]. It should be noted that the identification of HTLV-1 by means of amplification (polymerase chain reaction or PCR) techniques in monoclonal cells of the vitreous humor can also be performed.

Other diseases associated with the virus

Autoimmune diseases such as polymyositis, Sjögren's syndrome, thyroiditis, alveolitis and infectious dermatitis have been associated with HTLV-1 infection. La Grenade *et al.* (1990)[120] were the first to describe infectious dermatitis in Jamaica.

After this year, several cases of dermatological affection have been reported in endemic countries like Japan, Trinidad-Tobago, Colombia and Brazil. It commonly affects children and manifests as acute eczema with erythematous-papulocrostosis lesions, especially in the nasal vestibule. Other regions such as scalp, outer ear, armpits, retro-auricular and paranasal regions can be affected[121]. Spread of papular lesions may occur, and a chronic aqueous nasal discharge is frequent. Isolation of *Staphylococcus aureus* and *Streptococcus pyogenes* in cultures of nasal secretions and skin lesions[55]. The disease responds to the use of antibiotics, but the relapse occurs when the medication is withdrawn[19].

There is a predominance of infection by low virulent bacteria and frequent relapses due to the relationship between immunosuppression and infectious dermatitis[55]. As the age progresses, there is an improvement of the clinic, however, there may be development of ATLL or HAM/ TSP next[122].

Some studies suggest that HTLV infection may also be associated with immunosuppression and increase the risk of other infectious comorbidities. Hyperinfection by *Strongyloides stercoralis* present in patients infected with HTLV is explained by changes in the immune response, making possible a systemic dissemination of the infestation, which becomes recurrent, chronic and with a poor clinical response to the usual treatments[123,124]. Porto *et al.* (2005)[125] emphasized the possible protective effect of the strongyloid infestation in relation to the development of HAM/ TSP, resulting from a modulation of the Th1 response.

Treatment and prevention

There is still no cure for HTLV infection and treatment for patients with associated diseases requires considerable attention. Early studies that have brought initial responses to the existing gaps in the HTLV biological cycle are relatively recent and still need to be amplified. Patients with associated diseases usually have a slow or even asymptomatic clinical progression. When the initial symptoms of infection begin to manifest, the individual is often old enough, and few can get an accurate diagnosis in time to slow the progression of the disease. Prophylaxis is still the best form of prevention and the treatment has only the

function of improving to the maximum possible the quality of life of the individual[126].

Preventive measures should focus primarily on the orientation of at-risk groups, such as HIV positive donors, carrier mothers and injecting drug users. As the virus infects lymphocytes, cells in the blood, sexual secretions and breast milk, the HTLV carrier should be directed to: 1) Do not donate blood, semen or organs; 2) Do not share needles or syringes; 3) Do not breastfeed; 4) Use condoms in sex. If the couple is planning children, they will not just use the condom in the fertile time. It is necessary to clarify to the asymptomatic patient or to the patient that he / she can transmit HTLV, if he/ she does not adopt preventive measures[127].

Proietti (2015)[127] does reinforce that individuals who are carriers must communicate the test result to their sexual partners. These should be offered the chance to be tested and, finally, the children of positive mothers who have been breastfed by them also need to be tested.

4. DISCUSSION

Studies report the ignorance of the society, and even of the health professionals, about this infection, thus harming the correct counseling, treatment and adherence of public policies for an effective prevention. This neglect refers to the reality of being a long-term infection with latency and uncertain prognosis. The problem of "living with HTLV" is broad and complex, intervening in the daily lives of people with HIV, provoking often radical changes in lifestyle.

Although the prevention of viral dissemination of risk groups depends on the identification of cases in the population, HTLV infection is not currently considered a public health problem in Brazil and has been largely neglected for years. Regarding this fact, we agree with Costa *et al.* (2013)[73] when they say that "HTLV is an example of the major neglected infectious diseases that have been identified as priorities for research in Latin America and the Caribbean" and "In general, general ignorance of the virus increases the risk of transmission considerably."

Knowledge about HTLV needs to be more widespread among health professionals, since these are the agents that perform prevention and health promotion. Therefore, it is necessary to develop the sensitization of these professionals for the correct management to be carried out to prevent the virus, increasing their knowledge and raising the awareness of the population and health authorities to minimize the prevalence of infection in all Brazilian territory, besides making available the infant formula for the daughters of seropositive mothers for free and make compulsory notification for HTLV.

Therefore, it is confirmed by the results presented the importance of emphasizing that this infection should be considered a public health issue in the country, with greater exploitation of scientific production, analysis and discussion on HTLV for the development of health policies and strategies aimed at the carriers and health professionals who accompany these subjects.

5. CONCLUSION

The present study focused on the impact of HTLV-1 infection in the context of Public Health in Brazil. Despite the lack of knowledge about the virus, the uncertain implications of the prognosis for infected persons and their forms of transmission constitute a public health problem, especially in areas considered endemic, which needs attention.

In addition to being neglected and poorly understood when compared to other STIs, even with the efforts of central health agencies, the media also do little to spread disease-related issues.

As a result of the HTLV infection being mostly asymptomatic, it does not present any changes in visibly perceptible weaknesses in its patients and the reduced social knowledge of its complexities, it remains in the dark, and constitutes in the meantime a further challenge to the central public agencies of health professionals and professionals in the field of health education, promotion and prevention of the virus.

As a contribution of this study, it is suggested that the health services develop strategies that allow specific HTLV training to be carried out with professionals who work directly in the Family Health care. In addition, campaigns to prevent the sexual transmission of infection by other viruses, such as HIV and hepatitis, could have the addition of HTLV virus, so people know that by practicing safer sex, they will also avoid HTLV, in addition to those viruses known.

Finally, it is proposed to emphasize the importance of the screening of pregnant women in prenatal care services in Brazil, since they are mostly found without the possibility of being tested, since the infection does not have compulsory notification, and the screening is not part of the prenatal routine advocated by the Ministry of Health, thus ignoring the risk to which their children are exposed.

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