Immunopathogenesis and neurological manifestations associated to HTLV-1 infection

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ABSTRACT
The human T lymphotropic virus type-1 (HTLV-1) was the first human retrovirus identified. The virus is transmitted through sexual intercourse, blood transfusion, sharing of contaminated needles or syringes and from mother to child, mainly through breastfeeding2,3. The infection occurs predominantly in Africa, South America, the Caribbean and southeast Japan, with Brazil being significantly affected1,4.

The pathogenesis of HTLV-1 infection is not completely understood, but both T cell activation and proviral load are determinants of disease outcome. The two major diseases associated to the virus infection are adult T cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)5. These clinical manifestations occur in less than 5% of HTLV-1 infected patients and have been considered a low morbidity infection. However, several studies showed that a large number of HTLV-1 infected individuals develop symptoms of inflammatory disease6,7. Moreover, a large percentage of affected individuals have neurological symptoms other than HAM/TSP8.

In this review, the most recent data regarding pathogenesis and neurological manifestations of HTLV-1 infection were analyzed. Emphasis is given to immune response and the variety of neurological diseases associated with HTLV-1 infection.

INTRODUCTION
The human T lymphotropic virus type-1 (HTLV-1) was the first human retrovirus identified. The virus is transmitted through sexual intercourse, blood transfusion, sharing of contaminated needles or syringes and from mother to child, mainly through breastfeeding. In addition to the well-known association between HTLV-1 and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), several diseases and neurologic manifestations have been associated with the virus. This review was conducted through a PubMed search of the terms HTLV-1, immune response and neurological diseases. Emphasis was given to the most recent data regarding pathogenesis and clinical manifestations of HTLV-1 infection. The aim of the review is to analyze the immune response and the variety of neurological manifestations associated to HTLV-1 infection. A total of 102 articles were reviewed. The literature shows that a large percentage of HTLV-1 infected individuals have others neurological symptoms than HAM/TSP. Increased understanding of these numerous others clinical manifestations associated to the virus than adult T cell leukemia/lymphoma (ATLL) and HAM/TSP has challenged the view that HTLV-1 is a low morbidity infection.

Keywords: HTLV-1. Immune response. HAM/TSP. Neurologic disease.

For this review, we examined 398 articles from journals indexed in PubMed. The terms used for the research were: HTLV-1, immune response, HAM/TSP and neurological diseases associated with HTLV-1 infection. Of this total, 102 articles were selected.

STRUCTURE, GENOME AND PERSISTENCE OF THE HTLV-1
The HTLV-1 genome consists of a single-stranded ribonucleic acid (RNA). The two ends of the genome have long terminal repeats (LTRs) that help in the integration of proviral deoxyribonucleic acid (DNA) into chromosonal DNA. Structural and regulatory genes can be found between the LTRs. The proviral DNA, synthesized by reverse transcription of the viral RNA, has 9kb. The genes gag, pol and env encode structural proteins, and the gene tax encodes Tax, a regulatory protein. The Rex protein, encoded by the gene rex, promotes mRNA translation increasing proliferation and virus dissemination.

Recently, a new gene has been studied: HTLV-1 bZIP factor (HBZ). HBZ is found at the 3' end ofLTR and encoded by the complementary strand of the HTLV-1 genome. The HBZ messenger RNA (mRNA) is expressed in ATLL cells and its protein increases T cell proliferation. HBZ also participates in the pathogenesis of HAM/TSP as HBZ expression is directly correlated with proviral load.

HTLV-1 preferentially infects cluster of differentiation 4 (CD4+) T cells, but cluster of differentiation 8 (CD8+) T cells, dendritic cells, macrophages and other cells are also infected by the virus. The ubiquitous glucose transporter-1 (GLUT-1), neuropilin1 (NRP1) and surface heparan sulfate proteoglycans (HSPGs) function as receptors for cell invasion by the virus. Once inside the cell, the virus integrates its DNA into chromosomal DNA. The proviral DNA is transcribed into mRNA and structural proteins are synthesized, creating a new viral particle. Cell-to-cell transmission of HTLV-1 occurs through direct contact.
**IMMUNE RESPONSE TO HTLV-1**

The HTLV-1 infection causes a change in the intracellular environment, which leads to spontaneous activation of infected cells. The protein Tax is responsible for this activation, acting through the transcription nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB). Activated cells also actively transcribe interleukin-2 (IL-2) and interleukin-2 receptor (IL-2R) leading to intense cell proliferation, particularly T lymphocytes, and spontaneous cytokine production.

Spontaneous cytokine production is seen in both asymptomatic carriers and in patients with HAM/TSP. When compared with asymptomatic carriers, cells from individuals with HAM/TSP produces high levels of interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α). Elevated levels of chemokines CXCL10 and CXCL9 are also observed in patients with HAM/TSP. CD4+ and CD8+ T cells contribute in similar way to the spontaneous secretion of IL-2, IFN-γ and TNF-α in carriers and CD8 T cells are the main source of pro-inflammatory cytokines in HAM/TSP patients.

The cytokine profile in response to HTLV-1 infection shows a pattern of Th1 response, with increased TNF and IFN-γ production. However, mononuclear cells from asymptomatic carriers produce high levels of regulatory cytokines IL-5 and IL-10 when compared with seronegative individuals. The high IL-10 production in asymptomatic carriers may explain the clinical status of these individuals. The addition of IL-10 to culture of mononuclear cells from asymptomatic carriers decreases the production of IFN-γ. Such modulation is not observed when exogenous IL-10 is added to culture of mononuclear cell from patients with HAM/TSP.

Cytotoxic CD8+ T lymphocytes (CTL) are also important in the virus-triggered immune response. These cells are chronically activated, are able to recognize the viral protein Tax and are the main host defense mechanism in HTLV-1 infection. Progression of viral infection is able to recognize the viral protein Tax and are the main host defense triggered immune response. These cells are chronically activated, are and CD8 T cells are the main source of pro-inflammatory cytokines in way to the spontaneous secretion of IL-2, IFN-γ and TNF-α.

**IMMUNOPATHOGENESIS AND DISEASES ASSOCIATED WITH HTLV-1 INFECTION**

ATLL is an aggressive form of leukemia/lymphoma consisting of oligoclonal or monoclonal outgrowths of CD4+ and CD25+ T-cells. According to a Japanese study, the incidence rates of ATLL in HTLV-1 infected patients are 6.6% and 2.1% in male and female patients, respectively. Adult T cell leukemia/lymphoma is characterized by the presence of cellular infiltrates affecting the skin, liver, gastrointestinal tract and the lungs. Other characteristics of the disease include hypercalcemia and the presence of flower cells-leukemic cells with multilobulated nuclei on peripheral blood smear. HTLV-1 causes transformation due to the functional role of oncoproteins encoded in its genome. Of these, tax plays a major role in leukemogenesis of ATLL, particularly in the initiation of cellular transformation. Tax constitutively activates NFκB, which is important on leukemogenesis. Tax also contributes to cellular transformation by several other mechanisms, including chromosomal instability, amplification of centrosomes, inducing cell-cycle checkpoint derangements, loss of ability of DNA repair and inhibition of apoptosis in affected cells.

The Notch signaling pathway, which is involved in cellular proliferation, differentiation and apoptosis, is also activated in ATLL. Gamma-secretase inhibitors (which control the activation of Notch signaling) use triggered a reduction of tumor cells proliferation, showing the importance of this pathway in ATLL pathogenesis.

The pathogenesis of HAM/TSP is dependent upon both viral and immunological factors. In addition to high proviral load and pro-inflammatory environment discussed previously, HTLV-1 also interferes with cellular function by affecting regulatory T cells (CD4+CD25+Fox3+ T cells or T-reg cells). The virus infects T-reg cells and modifies its role in immune regulation. T-reg cell dysfunction coupled to lower production of regulatory cytokines prevents the immune system from down modulating lymphocyte activity in HTLV-1 infection. This impairment results in the secretion of high levels of pro-inflammatory cytokines and mediators damaging the spinal cord. Chemokines such as CXCL9 and CXCL10 are increased in the serum and in the cerebral spinal fluid of HTLV-1 carriers, and even more pronounced in HAM/TSP patients. These chemokines are responsible for the attraction of activated T cells to the central nervous system (CNS).

In a cross-sectional study comparing HTLV-1 carriers matched by age and sex with seronegative blood bank donors, Caskey et al. showed that xerostomy, periodontal disease, polyarthralgia, arthritis, erectile dysfunction and overactive bladder were significantly higher among HTLV-1 carriers than in controls. In the same study, it was shown that leg weakness, feet numbness, hipperreflexia of the inferior limbs and Babinski sign were also more frequent in HTLV-1 cases. Furthermore, uveitis, bronchitis and osteoporosis have also been associated with HTLV-1 infection. The relationship of these diseases with HTLV-1 has been further explored. For instance, HTLV-1 RNA has been documented in periodontal tissue of patients with chronic periodontitis associated to HTLV-1. Samples of periodontal tissue from patients diagnosed with...
HTLV-1 associated chronic periodontitis displayed a higher expression of IL-1β, IFN-γ and lower expression of Foxp3 and IL-10 than tissue from patients with chronic periodontitis not associated with the virus55.

HTLV-1 associated arthropathy needs to be better characterized both clinically and radiologically. A large number of HTLV-1 carriers as well as patients with HAM/TSP complain of arthralgias and, in a small subset of cases, arthritis is also documented5. In the majority of these individuals, the radiologic findings are consistent with osteoarthritis rather than rheumatoid arthritis. However, patients with HTLV-1 associated arthropathy have higher expression of pro-inflammatory cytokines such as TNF-α, IFN-γ and IL-6 in the synovial fluid66,67. The presence of these cytokines may be explained by the immunological response to the viral antigens at the site of inflammation.

In immunological studies in HTLV-1 infected patients with urinary manifestations of overactive bladder (OAB), immunological parameters were similar to those observed in patients with HAM/TSP. The immunologic features and proviral load in HTLV-1 carriers, HTLV-1 OAB and HAM/TSP are summarized on Table 1.

These data indicate that HTLV-1 infected patients with urinary manifestations of OAB have proviral load and levels of pro-inflammatory cytokines similar to that observed in HAM/TSP and higher levels than HTLV-1 carriers. These data suggest that HTLV-1 OAB is either an oligosymptomatic clinical form of HAM/TSP or an early stage of HAM/TSP.

**AUTO IMMUNITY VERSUS HYPERSENSITIVITY MEDIATED DISEASE IN HTLV-1**

As HTLV-1 may infect auto reactive cells, it is possible that expansion of these cell clones may lead to autoimmune disease. Several studies have associated HTLV-1 with rheumatoid arthritis, Sjögren’s syndrome and polymyositis among other diseases58. For instance, the prevalence of HTLV-1 was reported as 23% in patients with rheumatoid arthritis compared to 3.4% in the control group59. However, this association has not been confirmed by other studies56,61. Virus RNA has been documented in synovial tissue from HTLV-1 infected patients. In addition, increased level of pro-inflammatory cytokines is found in the synovial fluid of these patients. Thus, it is likely that hypersensitivity reaction against viral antigen in the synovium contributes to the joint damage in HTLV-1 associated arthropathy.

Dry mouth and to a less extent dry eyes are frequently documented in HTLV-1 infection. Thus, an association of HTLV-1 and Sjögren’s disease has been reported. This association was supported by the findings of lymphocyte infiltrates in affected salivary glands in HTLV-1 infected patients62. However, most patients lack other clinical features of Sjögren’s syndrome such as arthritis. Serological studies of these patients fail to show the presence of autoantibodies SS-A and SS-B, characteristic found in Sjögren’s syndrome63. On the other hand, sicca syndrome has been observed in several viral infections such as HIV and hepatitis C64. As there is no evidence of the presence of autoantibodies or auto reactive T cells in HTLV-1 infected patients diagnosed with sicca syndrome, it is likely that symptoms are caused by a hypersensitivity reaction rather than an autoimmune phenomenon.

**NEUROLOGICAL MANIFESTATIONS IN HAM/TSP**

HAM/TSP is caused by damage to the CNS structure, especially in the lower portion of the spinal cord65,66. Paraparesis, pyramidal signs and urinary symptoms signs are seeing in almost 100% of individuals with HAM/TSP, followed by sensory symptoms (50-78%). Other common complaints are pain and muscle atrophy67,68. The development of neurological disability in HAM/TSP occurs mainly during the first year of the disease, and subsequently it becomes relatively stable69. However, there are no spontaneous remissions70.


**NEUROLOGICAL MANIFESTATIONS OF HTLV-1 PATIENTS WITHOUT HAM/TSP**

In addition to HAM/TSP, other neurologic manifestations have been associated with the virus\(^{51}\). Some of these manifestations are related to spinal cord injury and are described as subclinical HAM/TSP like autonomic dysfunctions (overactive bladder, erectile dysfunction, blood pressure and heart rate dysregulation), pyramidal dysfunction (Babinski sign, hyperreflexia, spasticity) and sensory dysfunction (impaired vibratory and proprioceptive function). The WHO diagnostic criteria for HAM/TSP require both the presence of the clinical syndrome of paraparesis with autonomic and sensory abnormalities, positive HTLV-1 serology and confirmation of the presence of HTLV-1 in cerebral-spinal fluid (CSF)\(^{72}\). Some authors have proposed classifying patients with neurological symptoms not fulfilling the HAM/TSP criteria as possible or probable HAM/TSP\(^{73}\).

There are still other neurological symptoms not related to myelopathy such as cognitive dysfunction (cortical, ataxia (cerebellar), cranial mononeuropathy (cranial nerves), amyotrophic lateral sclerosis (ALS)-like syndrome (motor neuron), polyneuropathy (peripheral nerves) and myopathy (muscles). Some of these symptoms have being found in association with HAM/TSP\(^{68,74}\) and indicate that the HTLV-1 neurological disease is in fact more than a myelopathy. It is also an inflammatory disease of the entire nervous system.

**Autonomic involvement - The overactive bladder**

Overactive bladder is one of the most common neurologic presentations of myelopathy in patients without paraparesis\(^{75}\). Nocturia, urgency and incontinence are the most common urinary symptoms with a prevalence that can reach more than 20%\(^{67,78-81}\) (Table 2). Compared with seronegative controls, HTLV-1 carriers have higher frequency of urinary symptoms\(^{68,81}\). One study showed that the median length of bladder dysfunction was 61 months, and patients with urinary complaints had a higher median proviral load\(^{89}\).

Although overactive bladder has similar features of an urinary tract infection, a cross-sectional study that performed urine culture in HTLV-1 infected subjects concluded that urinary tract infection was present in a minority of cases and the majority of symptoms could be explained by overactive bladder syndrome\(^{82}\). Moreover, urodynamic studies found detrusor hyperreflexia in 37% and 22%\(^{83,84}\), detrusor hyporeflexia in 13%\(^{84}\) and detrusor sphincter dyssynergia in 11%\(^{83}\) of HTLV-1 patients without HAM/TSP. In some cases overactive bladder could precede HAM/TSP by years, being the initial manifestation of the disease\(^{81}\). The importance in the identification of those symptoms is that early treatment with anti-cholinergic and/or catheterization can be instituted and patients should be evaluated for other neurological manifestations.

**Autonomic involvement - erectile dysfunction**

Very few studies have evaluated the relationship between HTLV-1 and sexual complaints. Erectile dysfunction (ED) was found as an initial complaint in a 36 year-old HAM/TSP patient\(^{85}\). The prevalence of erectile dysfunction in the absence of HAM/TSP varies between 4 and 43% in the literature\(^{76,79}\) (Table 2). When compared with healthy controls, the prevalence in HTLV-1 patients is statistically higher\(^{4}\). Furthermore, the prevalence of ED is higher among patients with urinary symptoms and greater neurological disability (EDSS scale)\(^{76,86}\).

**Autonomic involvement - blood pressure and heart rate control**

HAM/TSP patients had an increase in heart rate and lower amplitude in blood pressure when compared with HTLV-1 patients without HAM/TSP and healthy controls\(^{87,88}\). In those cases there are both sympathetic and parasympathetic cardiovascular autonomic dysfunction\(^{88}\) and disturbance in sympathetic skin response\(^{87}\). Also there was correlation between the clinical symptoms and exam alterations\(^{87}\).

The low to high frequency ratio was significantly lower in HAM/TSP patients when compared to healthy controls and those
with thoracic cord atrophy had lower ratios, suggesting reduced cardiovascular sympathetic activity.

Isolated pyramidal signs

In the literature, hyperreflexia was found to be prevalent with a range from 4.6 to 34%78. Babinski sign was not common and has been seen in 6 to 10.4%78-81,90 (Table 2). Objective leg weakness is described in some studies and can reach a prevalence of 10%6,78,81,91. Some of those pyramidal signs appear as an isolated form and some combined with urinary and erectile dysfunction80, but not fulfilling the formal criteria for HAM/TSP. Interestingly in two cohort studies involving children with HTLV-1 a high prevalence of hyperreflexia was found and there was a strong relation with skin diseases (infective dermatitis, seborrhea, eczema) and anemia79,90.

Isolated sensory symptoms

To be compatible with diagnosis of myelopathy the sensory symptoms have to follow a specific pattern on physical examination. In the HAM/TSP criteria vibration sense is the modality with the most impairment, probably due to lesions in the dorsal columns of the spinal cord. Other symptoms like numbness and hand and feet paresthesias are more compatible with a polyneuropathy syndrome. A prevalence of 43.8% in vibration sense impairment was found in one study, which was statistically different from healthy subjects. In this study, however, trained nurses performed the physical exams rather than neurologists, which may have affected the prevalence estimate79.

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HAM/TSP and non-HAM/TSP HTLV-1 patients had a lower performance in neuropsychological tests when compared to controls. In HTLV-1 patients without HAM/TSP, impairment was found in verbal and visual memory, attention and visual motor abilities52. There was no association between brain magnetic resonance imaging findings and cognitive dysfunction assessed by the Mini-Mental State Exam in one small study93.

Cranial neuropathy

Few articles, generally case reports, have described an association between cranial neuropathy, usually facial nerve (VII cranial nerve) and HTLV-1. In one Caribbean study of 62 consecutive patients with facial nerve palsy the prevalence of HTLV-1 seropositivity was 20.7%94.

Cerebellar syndrome

Only case reports describe cerebellar manifestations in HTLV-1 patients. New onset loss of balance, wide-based stance and gait-truncal instability, and mild leg ataxia (vermian cerebellar syndrome), with absent upper limb dysmetria but with postural tremor, downbeat nystagmus, and dysarthria have been described81. In all cases, patients progressed to HAM/TSP characterizing a spinocerebellar syndrome95,96.

Amyotrophic lateral sclerosis - like syndrome

A few studies have found an association between amyotrophic lateral sclerosis (ALS)-like syndrome and HTLV-157. However, in those cases, the clinical presentation and progression of ALS-like syndrome was different than ALS, including long-term survival, absence of characteristic pathological findings (Bunina bodies in ALS) and presence of overactive bladder.

Polyneuropathy

A recent electrodiagnostic study in 73 patients with HAM/TSP found a prevalence of peripheral nerve involvement of 30%, with all patients demonstrating predominantly axonal neuropathy94. Sensory-motor polyneuropathy was the most common neuropathy observed in this study74. Investigators have reported a prevalence of 34% of peripheral nervous system involvement and 6% of polyneuropathy in patients without HAM/TSP98.

Myopathy

Two types of HTLV-1 associated myopathy have been described: inclusion body myositis99 and polymyositis100-102. Generally those patients do not present with HAM/TSP and response to treatment is poor99,100.

Conclusions

Advances in recent years have allowed to a better understanding of HTLV-1 infection and lead to a better characterization of its myriad associated clinical manifestations. Both the HTLV-1 virus and the failure of regulatory mechanisms in the immunological responses by the host immune system play a pivotal role in the maintenance of T cell activation. When T cell activation persists, tissue damage occurs. The recognition that the majority of HTLV-1 individuals have diseases other than HAM/TSP and ATLL and that a large percentage of HTLV-1 infected subjects previously considered carriers have neurological manifestations strongly suggest that HTLV-1 is associated with greater morbidity than previously thought.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABSTRACT IN PORTUGUESE

Imunopatogênesese manifestações neurológicas associadas à infecção pelo HTLV-1

O vírus linfotrópico de células T humanas do tipo 1 (HTLV-1) foi o primeiro retrovírus humano identificado. O vírus é transmitido via relações sexuais, transfusão de sangue, compartilhamento de agulhas ou seringas contaminadas ou da mãe para o filho, principalmente através da amamentação. Além da conhecida associação entre o HTLV-1 e a mielopatia associada ao HTLV-1 (HAM/TSP), várias doenças e manifestações neurológicas têm sido associadas com o vírus. Esta revisão de literatura foi conduzida através de pesquisa ao banco de dados do PubMed, com os termos HTLV-1, resposta imune e doenças neurológicas. Foram enfatizados os dados mais recentes sobre a patogênese e às manifestações clínicas na infecção pelo HTLV-1. O objetivo dessa revisão é analisar a resposta imune e a variedade de manifestações neurológicas associadas com a infecção pelo HTLV-1.
Um total de 102 artigos foi analisado. A literatura mostra que grande porcentagem de indivíduos infectados pelo HTLV-1 apresenta sintomas neurológicos mesmo na ausência de HAM/TSP. Uma maior compreensão das várias manifestações clínicas associadas ao vírus, além da leucemia/filíma de células T do adulto (ATLL) e HAM/TSP, auxilia a estabelecer que, na realidade, a infecção pelo vírus possui uma morbidade maior do que se pensava.

**Palavras-chaves:** HTLV-1. Resposta imune. HAM/TSP.

**Doença neurológica.**

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