

# Neurologic complications of HTLV-1: a review.

## *Complicações neurológicas do HTLV: uma revisão HTLV-1*

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### ABSTRACT

The human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus that infects about 20 million people worldwide and causes immune-mediated diseases of the nervous system. The classical neurological presentation of HTLV-1 infection is the so-called HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). However, HAM/TSP is not the only neurological outcome that can result from HTLV-1 infection. In this Review it is made an update on the many aspects of this important neurological condition, the HTLV-1 neurological complex.

Key-words: HTLV-1, tropical spastic paraparesis, HTLV-1-associated myelopathy

### RESUMO

O vírus linfotrópico de células T humanas tipo 1 (HTLV-1) é um retrovírus que infecta cerca de 20 milhões de pessoas em todo o mundo e causa doenças imunomediadas do sistema nervoso. A apresentação neurológica clássica da infecção pelo HTLV-1 é a chamada paraparesia espástica tropical / mielopatia associada ao HTLV-1 (HAM/TSP). HAM / TSP, no entanto, não é o único desfecho neurológico que pode resultar da infecção pelo HTLV-1. Nesta revisão, é feita uma atualização sobre vários aspectos desta importante condição neurológica, o complexo neurológico do HTLV-1.

Palavras-chave: HTLV-1, paraparesia espástica tropical, mielopatia associada ao HTLV-1

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## INTRODUCTION

The human T cell lymphotropic virus type 1 (HTLV-1) was the first human retrovirus to be discovered and belongs to the Retroviridae family, the Orthoretrovirinae subfamily and to the deltaretrovirus genus<sup>1</sup>. HTLV-1 preferentially infects CD4+CCR4+ effector/memory T cells *in vivo*<sup>2</sup>.

HTLV-1 is the causative agent of a variety of diseases including adult T-cell leukemia/lymphoma (ATLL)<sup>3</sup> and the HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)<sup>4</sup>. ATLL is due to a neoplastic clonal growth of HTLV-1-infected CD4 positive T-cells and is characterized by unique clinical features including hypercalcemia and severe organ infiltration of leukemic cells. HAM/TSP is an immune-mediated disease of the central nervous system (CNS) but the precise mechanism for disease development is still a matter of debate<sup>5</sup>.

## EPIDEMIOLOGY

The most endemic regions to HTLV-1 are the Southwestern part of Japan, sub-Saharan Africa, South America, the Caribbean area, and some foci in the Middle East and Australo-Melanesia. HTLV-1 can be transmitted through breastfeeding, sexual intercourse, and contact with contaminated cellular blood products. The HTLV-1 prevalence increases gradually with age, especially among women. Nowadays it is estimated the total number of HTLV-1 carriers to vary between 10-20 million individuals<sup>6</sup>.

In contrast to HIV-1 infection, where most patients end up with AIDS, only 2%-3% of infected persons develop ATLL and other 0.25%–3.8% develop HAM/TSP, while the majority of infected individuals remain lifelong asymptomatic carriers (ACs). Apparently host and virological factors play a role in the neurological outcome once an individual becomes infected<sup>5,6</sup>.

## PATHOPHYSIOLOGY

To date the best predictor of becoming ill is a high HTLV-1 proviral load (PVL), in other words, the percentage of peripheral blood mononuclear cells (PBMCs) that carry the provirus. In Japanese studies the median PVL was more than 10 times higher in HAM/TSP patients than in asymptomatic carriers (ACs)<sup>7</sup>. Studies from the Caribbean, South America, and the Middle East replicated these findings. Apparently genetic factors such as the human leukocyte antigen (HLA) genotype are related to the high

PVL in HAM/TSP patients and genetic relatives. In chronic HTLV-1 infection about 90–95% of the PVL is carried by CD4+ T cells and 5–10% by CD8+ T cells<sup>5</sup>.

HAM/TSP is characterized by an over-stimulation of the immunologic compartment, including increased expression of a repertoire of inflammatory cytokines and chemokines, and an increase in the number of highly activated circulating CD8+ T cells directed against the Tax11-19 viral epitope in both peripheral blood (PB) and cerebrospinal fluid (CSF)<sup>5</sup>.

The real mechanisms by which HTLV-1 induces neurological diseases remain unknown so far. The main hypothesis to explain HAM/TSP neuropathogenesis is the so-called Bystander damage. It suggests that the presence of interferon-gamma-secreting HTLV-1-infected CD4+ T cells and their recognition by virally specific cytotoxic T CD8 CTL in the CNS induce microglia to secrete some cytokines, such as TNF- $\alpha$ , which may be toxic for myelin. Both anatomically determined hemodynamic conditions and adhesion molecule-mediated interactions between circulating infected T cells and endothelial cells may contribute to the localization of the main lesions. Following an induction of the HTLV-1 antigens on the surface of infected T cells in CNS compartment, expansion of the responses of immunocompetent T cells against the viral proteins may result in CNS tissue damage that may be mediated by released cytokines. More recently some investigators advocated the possibility of the existence of a continuous positive feedback loop via astrocytes that would maintain a state of chronic inflammation of the spinal cord in HAM/TSP. Accordingly, HTLV-1-infected cells in the CNS would produce interferon-gamma that would induce astrocytes to secrete the chemokine CXCL10, which would be able to recruit more infected cells to the area via the chemokine receptor CXCR3, constituting a T helper type 1-centric positive feedback loop that would result in a state of chronic inflammation<sup>8</sup>.

In necropsy cases of Japanese HAM/TSP the spinal cord shows symmetrical atrophy especially of the thoracic cord proportionally to the severity of neurological deficits. Infiltration of mononuclear cells and degeneration of both myelin and axons are the essential microscopical findings of cases with relatively short clinical course of the disease. Inflammatory lesions are most severe in the middle-lower thoracic spinal cords and extend throughout the entire spinal cord. Similar but milder lesions are seen scattered in the brain. In patients with a more prolonged

clinical history, the spinal cord shows a monotonous degeneration and gliosis with a few inflammatory cells in the perivascular areas. Fibrous thickening of the vessel walls and pia mater are frequently noted. These findings suggest a preceded inflammatory process in such areas. Degeneration of the spinal cord white matter is symmetric and diffuse but more severe at the antero-lateral column and inner portion of the posterior column where the inflammatory lesions are accentuated in the active-chronic phase. There are no focal demyelinating plaques. HTLV-1 proviral DNA can be detected in extracted DNA from affected spinal cord in HAM/TSP by PCR. The amount tends to decrease with the disease progression and this decline is paralleled with the decrease of CD4+ T-cell numbers<sup>9</sup>.

Some authors outside Japan put less importance on the inflammatory component of these lesions. They speculate that in their autopsy cases the neuraxis affected in a more systemic axial fashion as seen in neurodegenerative diseases, and the lesions did not seem to be secondary to vascular or inflammatory abnormalities, as proposed by the Japanese<sup>10</sup>.

Cases with other neurological manifestations of HTLV-1 infection who have been submitted to pathological examination showed a variety of findings such as various degrees of inflammatory changes with necrotic and degenerating muscle fibers and focal invasion of HTLV-1 infected CD4+ cells (mainly) in HTLV-1-associated myositis; anterior horn cell loss with surrounding infiltration of CD8+ lymphocytes, gliosis, axonal and myelin loss of the pyramidal tracts in all spinal cord levels, and thickened and infiltrated leptomeninges in those ALS-like cases; and a combination of both demyelination/remyelination and axonal degeneration/regeneration or, less often, the presence of inflammatory infiltrates in the peripheral nerves in those patients with polyneuropathy<sup>5</sup>.

## **CLINICAL FEATURES OF THE HTLV-1-ASSOCIATED NEUROLOGICAL COMPLEX<sup>11</sup>**

- HAM/TSP<sup>12</sup>: is a neurological condition still defined clinically and serologically in accordance with guidelines proposed by a W.H.O. panel of experts in 1988. These guidelines, although still largely employed, have some important shortcomings. Several vague terms are used frequently and the criteria are far from being stringent, encompassing many syndromes into a single one. This led to a proposal of new diagnostic guidelines that classified the disease according to different sublevels of

ascertainment (Table 1)<sup>13</sup>.

HAM/TSP is a slowly progressive disease. Some large prospective studies show that patients progressed from disease onset to wheelchair confinement over a median of 21 years<sup>14,15</sup>.

Although HAM/TSP is certainly the tip of the iceberg of the HTLV-1 associated neurological complex other neurological syndromes can be found in HTLV-1 positive individuals without myelopathy or, more often, in association with HAM/TSP. This implies that the neurological spectrum of HTLV-1 might be broader than previously thought.

### **-HTLV-1 ASSOCIATED POLYMYOSITIS (HAPM)<sup>16,17</sup>:**

Although isolated HAPm has been described, most published cases are associated with HAM/TSP. HAPm is an important diagnosis to bear in mind if patients with HAM/TSP start to develop a new pattern of muscular weakness (more proximal), myalgias, and increased creatine kinase (CK) levels. Compared to idiopathic polymyositis, HAPm follows a more protracted course and is particularly resistant to steroids.

### **- HTLV-1 ASSOCIATED POLYNEUROPATHY (HAPN)<sup>18-20</sup>:**

Peripheral neuropathies have been consistently found in association with HAM/TSP. The clinical picture is of paresthesias, burning sensations, and abnormal superficial sensation distally in a stock and glove distribution, generally associated with abolished ankle jerks. Although in most cases the peripheral nerve involvement is associated with HAM/TSP they can also be found in isolation, without any accompanying sign of spinal cord involvement. When present, these isolated HAPn manifest mostly as a predominantly sensory axonal polyneuropathy.

### **- HTLV-1 ASSOCIATED DYSAUTONOMIA (HAD)<sup>21,22</sup>:**

Autonomic disturbances are always associated with HAM/TSP and so far have never been described in isolation. It is characterized by impairment of cardiovascular and sweat control, and clearly indicates a major dysfunction of the sympathetic nervous system. Postural hypotension is a common feature of HAM/TSP and should always be investigated and treated symptomatically. Perhaps the dysautonomia is more frequent than previously suggested, and in some cases may be severe enough to warrant specific treatment. Cardiovascular autonomic dys-

function in HAM/TSP patients is mainly associated with cardiac sympathetic efferent abnormalities in the upper thoracic segments.

### **- AMYOTROPHIC LATERAL SCLEROSIS-LIKE SYNDROME ASSOCIATED WITH HTLV-1 (ALS-HTLV)<sup>23-25</sup>:**

Amyotrophic lateral sclerosis (ALS) is a progressive, invariably fatal neurologic disorder resulting from upper and lower motor neuron degeneration, which typically develops during the sixth or seventh decade of life, and is diagnosed based on standard clinical criteria. Its underlying cause remains undetermined. The disease may occur with increased frequency within certain families, often in association with specific genomic mutations, while some sporadic cases have been linked to environmental toxins or trauma. Another possibility, first proposed in the 1970s, is that retroviruses play a role in pathogenesis.

Amyotrophic lateral sclerosis-like pictures have been occasionally described as a sole manifestation of HTLV-1 infection. The main difference between these patients and the typical HTLV-1 negative ALS cases is the longer evolution and slower progression of HTLV-1 infected individuals.

### **-CHRONIC DIFUSE ENCEPHALOMYELOPATHY, ENCEPHALITIS AND COGNITIVE DEFICITS:**

Diffuse brain white matter MRI abnormalities, reflecting a chronic perivascular inflammation with progressive gliosis can explain the mild cognitive disturbance reported in some HTLV-1-infected individuals, with psychomotor slowing and deficits in verbal and visual memory, attention, and visuomotor abilities<sup>26</sup>. Imaging and autopsy studies IN HAM/TSP also demonstrate brain inflammation. In general, this is subclinical. More recently, patients with reduced consciousness, fever/hypothermia, headaches, seizures, and focal neurological signs have been described in association with HTLV-1 infection. Histopathology showed perivascular predominantly CD8+ lymphocytic infiltrates in the brain<sup>27</sup>.

### **INVESTIGATIONS**

A variety of systemic laboratory abnormalities can be found in patients with HAM/TSP, such as the presence of “flowers cells” (atypical lymphocytes with petal shape nuclei, typical of ATLL), hypergammaglobulinemia,

increased proportion of CD4+ to CD8+ cells, presence of autoantibodies and false-positive serologic tests, such as VDRL and Lyme serology. A higher PVL in the blood seems to be able to distinguish HAM/TSP from those asymptomatic carriers, as well as those individuals with a more rapid disease progression<sup>5</sup>.

The CSF may be normal or reveal a small/moderate mononuclear pleocytosis along with a modestly elevated protein content. In addition, oligoclonal IgG bands, increased levels of cytokines (neopterin, TNF- $\alpha$ , IL-6 and IL- $\gamma$ ), and increased intrathecal antibody synthesis specific for HTLV-1 antigens have also been described. Some authors have advocated the use of PVL measurement in the CSF as a diagnostic method to help in the definition of HAM/TSP<sup>15,28</sup>, although there is no agreement about that<sup>29</sup>. Accordingly, the percentage of HTLV-1-infected cells in the CSF cells and the CSF/PBMC HTLV-1/PVL ratio are always >10% and >1, respectively, in patients with HAM/TSP in contrast to <10% and <1, respectively, in asymptomatic carriers.

As mentioned, the PVL is higher in the blood of HAM/TSP than in asymptomatic carriers. PVL values vary widely between individuals, but are relatively constant within individuals.

Cerebral white matter lesions and spinal cord abnormalities have been frequently observed in HAM/TSP. Sometimes, early in the course of the myelopathy, one can find spinal cord edema, reflecting an active inflammatory process. As the disease progresses the spinal cord becomes progressively atrophic<sup>30</sup>.

### **DIFFERENTIAL DIAGNOSIS**

HAM/TSP can be occasionally mistaken for other neurological conditions such as the “progressive” spinal form of multiple sclerosis, the vacuolar myelopathy of AIDS, sporadic cases of familial spastic paraparesis, primary lateral sclerosis, some slowly progressive spinal cord compressions, vitamin B12 or copper deficiency, idiopathic transverse myelitis, Lyme disease, and neurosyphilis<sup>31</sup>.

Most of these conditions can be ruled out by an initial screening with a brain and spinal magnetic resonance imaging (MRI), CSF examination, and specific blood tests.

### **MANAGEMENT AND TREATMENT**

HAM/TSP is a highly incapacitating myelopathy, but clinical trials of specific drugs to treat it are lacking.



Oral or intravenous corticosteroids are still the mainstay of HAM/TSP treatment, particularly in the initial phase of the disease, when inflammation is more prominent than demyelination and gliosis<sup>32</sup>. Motor disability, pain, and urinary dysfunction may be ameliorated with steroids, but improvement is usually not sustained in most of the patients<sup>5</sup>.

Since HAM/TSP is associated with a high HTLV-1 PVL, reducing this load could treat or even prevent disease. However, despite *in vitro* evidence that certain nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs) are active against HTLV-1, *in vivo* results have been disappointing showing no clinical improvement or reduction of the PVL<sup>33</sup>. Valproic acid as a potential treatment for HAM/TSP based on evidences showing that this drug can activate viral gene expression and expose virus-infected cells to the immune system, leading to a reduction of the PVL. Despite these theoretical advantages the drug resulted ineffective to improve motor and other disabilities<sup>34</sup>. Other drugs such as interferon-alpha, cyclosporin A, methotrexate, pentoxifylline, azathioprine, and danazol may be tried if steroids fail or cannot be tolerated, but their use should be balanced in terms of their individual risk-benefit profile<sup>5</sup>.

Symptomatic treatment employing drugs and physical therapy to alleviate pain - which strongly correlates with a low quality of life of these individuals -, spasticity and to improve bladder control, are nowadays the mainstay in the treatment of HAM/TSP<sup>35</sup>.

## CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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Table 1. Diagnostic Guidelines for HAM/TSP according to levels of ascertainment 13

<p><b>Definite</b></p> <ol style="list-style-type: none"> <li>1. A non-remitting progressive spastic paraparesis with sufficiently impaired gait to be perceived by the patient. Sensory symptoms or signs may or may not be present. When present, they remain subtle and without a clear-cut sensory level. Urinary and anal sphincter signs or symptoms may or may not be present.</li> <li>2. Presence of HTLV-1 antibodies in serum and CSF confirmed by Western blot and/or a positive PCR for HTLV-1 in blood and/or CSF.</li> <li>3. Exclusion of other disorders that can resemble TSP/HAM</li> </ol>
<p><b>Probable</b></p> <ol style="list-style-type: none"> <li>1. Monosymptomatic presentation: spasticity or hyperreflexia in the lower limbs or isolated Babinski sign with or without subtle sensory signs or symptoms, or neurogenic bladder only confirmed by urodynamic tests.</li> <li>2. Presence of HTLV-1 antibodies in serum and/or CSF confirmed by Western blot and/or a positive PCR for HTLV-1 in blood and/or CSF.</li> <li>3. Exclusion of other disorders that can resemble TSP/HAM.</li> </ol>
<p><b>Possible</b></p> <ol style="list-style-type: none"> <li>1. Complete or incomplete clinical presentation.</li> <li>2. Presence of HTLV-1 antibodies in serum and/or CSF confirmed by Western blot and/or a positive PCR for HTLV-1 in blood and/or CSF.</li> <li>3. Disorders that can resemble TSP/HAM have not been excluded.</li> </ol>

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