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CENTRAL NERVOUS SYSTEM INFECTIONS (J LYONS, SECTION EDITOR)

Update on Neurological Manifestations of HTLV-1 Infection

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Abstract The human T cell lymphotropic virus type 1 (HTLV-1) is a retrovirus that infects 10–20 million persons around the world. Initially associated with the hematological malignancy adult T cell leukemia/lymphoma (ATLL), HTLV-1 is also the cause of a chronic progressive myelopathy named "HTLV-1-associated myelopathy/tropical spastic paraparesis" (HAM/TSP). HAM/TSP arises as the tip of the iceberg of an assortment of neurological syndromes triggered by the virus such as inflammatory myopathies, polyneuropathies, amyotrophic lateral sclerosis (ALS)-like syndromes, dysautonomia, and cognitive impairment. HAM/TSP typifies a chronic progressive spastic paraparesis with neurogenic bladder and minimal sensory signs. The neuropathology of HAM/TSP is concentrated in the thoracic spinal cord and is typically biphasic. Initially, there is a perivascular lymphocytic cuffing and mild parenchymal mononuclear infiltrates. Subsequently, this is replaced by gliosis and scarring. The neuropathogenesis of HTLV-1 is still partially understood. At present, the therapy of HAM/TSP remains basically symptomatic.

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Introduction

The human T cell lymphotropic virus type 1 (HTLV-1) was the first human retrovirus to be discovered and is the causative agent of a variety of diseases including adult T cell leukemia/lymphoma (ATLL), HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), and other systemic inflammatory conditions such as uveitis (HU), infectious dermatitis, and other diseases with yet poorly proven association such as arthropathy, pneumopathy, and exocrinopathy. ATLL is due to a neoplastic clonal growth of HTLV-1-infected CD4-positive T cells and is characterized by distinctive clinical features including hypercalcemia and severe organ infiltration of leukemic cells [1]. 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 discussion [2]. The simultaneous occurrence of HAM/TSP and ATLL is unusual although it has been reported in some cases [3].

HTLV-1 belongs to the *Retroviridae* family, to the *Orthoretrovirinae* subfamily, and to the *Deltaretrovirus* genus. $CD4^+$ lymphoid cells are the main cells infected in vivo. The transfer of the virus from an infected cell to a target cell can occur through the formation of a viral synapse and/or by a virofilm structure. Three molecules have been identified for binding and/or entry of HTLV-1: heparan sulfate proteoglycans, neuropilin-1, and glucose transporter 1. The HTLV-1 genome has three major open reading frames (ORFs) (gag, pol, and env) coding structural and enzymatic proteins. HTLV-1 encodes also some regulatory and auxiliary proteins such as the tax protein with transforming activities and the HTLV-1 basic leucine

zipper factor (HBZ) protein that plays a role in the proliferation and maintenance of the leukemic cells [4].

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 steadily with age, especially among women. Nowadays, it is estimated the total number of HTLV-1 carriers to vary between 5 and 20 million individuals [5]. This huge discrepancy is probably due to poor seroepidemiological data and the lack of reliable epidemiological information in highly populated regions.

In contrast to HIV-1 infection, where most patients end up with AIDS, only 2–3 % of infected individuals develop ATLL and other 0.25–3.8 % develop HAM/TSP. The majority of infected individuals will remain asymptomatic carriers (AC) for their lives [6]. This remarkable difference between these two neuropathogenic retroviruses has puzzled investigators for many years. Apparently, host and virological factors play a role in the neurological outcome once an individual becomes infected.

The best predictor of having either HAM/TSP or ATLL is a high HTLV-1 proviral load (PVL), viz., the percentage of peripheral blood mononuclear cells (PBMCs) that harbor the provirus. In Japanese studies, the median PVL was more than ten times higher in HAM/TSP patients than in AC. Studies from the Caribbean, South America, and the Middle East replicated these findings. It seems that genetic factors such as the human leukocyte antigen (HLA) genotype have a crucial impact on the high PVL in HAM/TSP patients and their relatives. In the Japanese population, for example, the possession of the HLA class I genes HLA-A*02 and Cw*08 was related with a statistically significant reduction in both HTLV-1 PVL and the risk of HAM/TSP. On the other hand, the possession of HLA class I HLA-B*5401 and class II HLA-DRB1*0101 predisposes to HAM/TSP in the same population. Because the function of class I HLA proteins is to present antigenic peptides to cytotoxic T lymphocytes (CTLs), these results indicate that individuals with HLA-A*02 or HLA-Cw*08 mount a particularly efficient CTL response against HTLV-1, which may be an important determinant of HTLV-1 PVL and the risk of HAM/TSP. In other words, these findings imply that the CTLs against HTLV-1 decrease PVL and the risk of HAM/TSP [7]. In chronic HTLV-1 infection, $CD4^+$ T cells carry approximately 90–95 % of the PVL whereas $CD8^+$ T cells carry 5–10 %. Still, a significant proportion of infected individuals who have a high HTLV-1 PVL will never develop disease, implying that additional factors contribute to HTLV-1-associated diseases.

Apparently, non-HLA gene polymorphisms also influence the chance of having HAM/TSP. For instance, the TNF-α promoter -863 A allele and the longer CA repeat alleles of matrix metalloproteinase (MMP)-9 promoter predisposed to HAM/TSP, whereas IL-10-592 A, stromal-derived factor (SDF)-1 +801A, and IL-15 +191 C alleles protected from developing the disease. To date, the contributions of these non-HLA genes to the pathogenesis of HAM/TSP are essentially unknown, and these data have not yet been replicated in other populations [6].

Although most studies of the HTLV-1 genotype have reported no association between variants of HTLV-1 and the risk of HAM/TSP, some authors described the association between HTLV-1 *tax* gene variation and the risk of HAM/TSP [8].

In persons with a high frequency of spontaneous proviral expression in vitro, HTLV-1 was frequently found integrated in transcriptionally active units of the genome. In healthy carriers, the provirus was mainly integrated in transcriptionally silenced parts of the genome, whereas integration into transcriptionally active units and subsequently increased expression of the provirus made individuals more liable to HAM/TSP. Yet, this distribution of genomic integration sites in vivo represents the consequence of many years of selection in which proviral expression that drives viral spread is compensated by the host immune response, predominantly by the CTL reaction to the virus [9].

The most accepted neuropathogenic view on HAM/TSP suggests an overstimulation of the immunologic system, with an amplified expression of a variety of inflammatory cytokines and chemokines, HTLV-1 Tax protein and gp46-specific antibodies directed against a number of cellular elements, and an increased number of highly activated circulating $CD8^+$ T cells directed against the $Tax_{11\text{-}19}$ epitope in both peripheral blood (PB) and cerebrospinal fluid (CSF). Both $CD4^+$ and $CD8^+$ T cells tend to accumulate in lesions of the spinal cord in the initial stages of the disease, whereas in more chronic phases, $CD8^+$ T cells are the predominant cellular infiltrate. It has been shown that in some HLA-A*201 HAM/TSP patients, the frequency of $Tax_{11\text{-}19}$-specific CTLs is as high as 20 % of all $CD8^+$ T cells in the PB and even higher in the CSF [10].

The real mechanisms by which HTLV-1 causes neurological diseases remain a mystery. Three main hypotheses have been considered as the most probable [11]:

1. *Direct toxicity*: glial cells infected by HTLV-1 and expressing viral antigens on their surface are recognized and attacked by anti-HTLV-1-specific $CD8^+$ CTLs which have crossed the blood-brain barrier (BBB). These activated CTLs react mainly against the *tax* protein and during their attack release cytokines that are harmful to neurons and the glia.
2. *Autoimmunity*: a "self" antigen similar to an HTLV-1 antigen and expressed by a glial cell is mistakenly recognized by an activated $CD4^+$ T helper cell which reacts against it through an autoimmune response that results in the glial cell death.

3. *Bystander damage*: the recognition, within the CNS, of interferon-gamma-secreting HTLV-1-infected $CD4^+$ T cells by virally specific cytotoxic T CD8 CTLs induces microglia to secrete some cytokines, such as TNF-alpha, which are myelinotoxic. 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 in the thoracic cord. Following an induction of the HTLV-1 antigens on the surface of infected T cells in the CNS compartment, expansion of the responses of activated T cells against the viral proteins results in CNS tissue damage which is mediated by the release of cytokines [12].

The direct toxicity theory has not been supported through in vivo evidences to date. Yet, the remaining theories could still play a role in the CNS damage. Another possibility is that CTLs recognize viral products presented by HTLV-1-infected vascular endothelial cells or other infected T cells. This would result in CTL activation and subsequent cytokine secretion.

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. According to this hypothesis, 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 [13].

The HTLV-1-Associated Neurological Complex

HAM/TSP HAM/TSP is a neurological condition still defined clinically and serologically in accordance with guidelines suggested by a panel of experts in 1988 (see ref. [14] for details). These guidelines, although still largely employed, have some important weaknesses. Several imprecise expressions are used frequently and the criteria are far from being strict, embracing many syndromes into a single one. This led to a proposal of new diagnostic recommendations that classified the illness according to different sublevels of ascertainment (Table 1).

HAM/TSP is a slowly progressive disease. In a study of 123 patients with a 14-year follow-up, patients progressed from disease onset to wheelchair confinement over a median of 21 years [16].

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 [2].

Table 1 "New" diagnostic guidelines for HAM/TSP according to levels of ascertainment

Definite
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.
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.
3 Exclusion of other disorders that can resemble HAM/TSP.
Probable
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.
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.
3 Exclusion of other disorders that can resemble HAM/TSP.
Possible
1 Complete or incomplete clinical presentation.
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.
3 Disorders that can resemble HAM/TSP have not been excluded.

Adapted from [15]

HTLV-1-Associated Polymyositis (HAPm) 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 [17, 18].

HTLV-1-Associated Polyneuropathy (HAPn) 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 [19].

HTLV-1-Associated Dysautonomia (HAD) 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 selected cases may be severe enough to deserve specific treatment [20, 21].

Amyotrophic Lateral Sclerosis-Like Syndrome Associated with HTLV-1 (ALS-HTLV) 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 Diffuse Encephalomyelopathy Diffuse brain white matter magnetic resonance imaging (MRI) abnormalities, reflecting a chronic perivascular inflammation with progressive gliosis [22], 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 [23].

Laboratory Tests

A variety of systemic laboratory abnormalities can be found in patients with HAM/TSP, such as the presence of "flower cells" (atypical lymphocytes with petal-shaped nuclei, typical of ATLL), hypergammaglobulinemia, increased proportion of $CD4^+$ to $CD8^+$ cells, presence of various 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 [24].

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-α, IL-6, and IL-γ), and increased intrathecal antibody synthesis specific for HTLV-1 antigens have also been described. More recently, some authors have advocated the use of PVL measurement in the CSF as a diagnostic method to help in the definition of HAM/TSP [25]. According to their experience, 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 already 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 [26]. 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.

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 B_{12} or copper deficiency, idiopathic transverse myelitis, and neurosyphilis.

Most of these conditions can be ruled out by an initial screening with a brain and spinal MRI, CSF examination, and specific blood tests. MRI abnormalities in HAM/TSP are mostly confined to the cervical and thoracic cords. In more acute or recent-onset disease, one can see cord enlargement sometimes with contrast enhancement, which is gradually replaced by unenhanced cord atrophy (Figs. 1 and 2, with permission [27]).

Neuropathological Findings

In necropsy cases of Japanese HAM/TSP cases, the spinal cord showed symmetrical atrophy particularly in the thoracic cord. These lesions were proportional to the severity of neurological deficits. Infiltration of mononuclear cells and

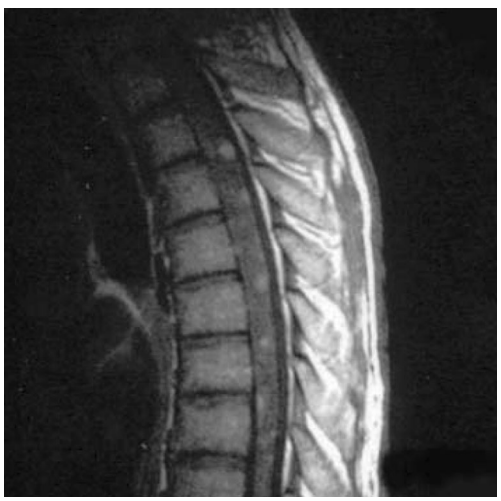

Fig. 1 MRI (sagittal T1-weighted sequence) showing thoracic spinal cord swelling with contrast-enhanced foci

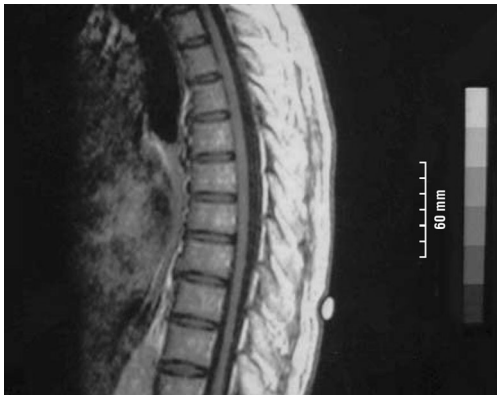

Fig. 2 MRI (sagittal T1-weighted) showing thoracic cord atrophy without enhancement

degeneration of both myelin and axons were the essential microscopical findings of cases with relatively short clinical course of the disease. Inflammatory lesions were most severe in the middle-lower thoracic spinal cords extending throughout the entire cord. Milder lesions were seen scattered in the brain. Monotonous degeneration and gliosis with a few inflammatory cells in the perivascular areas of the spinal cord could be seen in patients with a more prolonged clinical history. Fibrous thickening of the vessel walls and pia mater was frequently noted, which suggests the existence of a preceded inflammatory process. Degeneration of the spinal cord white matter was symmetric and diffuse but more severe at the anterolateral column and inner portion of the posterior column where the inflammatory lesions were accentuated in the active-chronic phase. Wallerian-type fascicular degeneration was superimposed. No focal demyelinating plaques could be detected. Although gliosis was also observed in the spinal cord gray mater, neuronal cells were relatively preserved [28]. In patients with illness of shorter duration, $CD4^+$ and $CD8^+$ cells along with macrophages were evenly distributed in the active inflammatory lesions. Instead, there was a predominance of $CD8^+$ cells over $CD4^+$ cells in the inactive-chronic lesions in patients with a longer duration of the illness.

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 [29].

Although these seminal descriptions from Japan emphasize the inflammatory aspect of HAM/TSP, other authors disagree with that, based in their own autopsied cases. This is the case, for instance, of Cartier et al. [30] who described a somatotopic distribution of lesions following a "dying back" ascendant and descendant distribution. Although abnormal vessels with gross thickening of the adventitia, many of them with lymphocytic cuffs, were seen, especially in the spinal cord, brain stem, midbrain and meninges, there was no correlation between these findings and the parenchymal lesions. The authors speculate that in these cases, the lesions affected the neuraxis in a more systemic axial fashion as seen in neurodegenerative diseases, and they did not seem to be secondary to vascular or inflammatory abnormalities, as proposed by many.

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 [31]; 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 [32, 33]; and a combination of both demyelination/remyelination and axonal degeneration/regeneration [34] or, less often, the presence of inflammatory infiltrates in the peripheral nerves in those patients with polyneuropathy [19].

Management and Treatment

In spite of HAM/TSP being a common and extremely disabling illness [35], clinical trials of specific drugs to treat it are lacking. The shortage of good therapeutic studies on this condition can be explained, at least in part, by a combination of reasons such as difficulty in enrolling patients in early phases of the disease, inadequate measurement tools to evaluate neurologic improvement, and even lack of interest of investigators from more developed countries to be involved in such trials. Oral or intravenous corticosteroids are still the basis of HAM/TSP treatment, particularly in the initial phase of the disease, when inflammation is more prominent than demyelination and gliosis. Motor disability, pain, and urinary dysfunction may be improved with steroids, but this improvement is usually not sustained in most of the patients [36].

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 analog reverse transcriptase inhibitors (NRTIs) are active against HTLV-1, in vivo results have been disappointing showing no clinical improvement or reduction of the PVL [37, 38]. The same is true for integrase inhibitors such as raltegravir. Although in vitro studies support that they may inhibit HTLV-1 replication, this has not been confirmed in vivo. The lack of continuous viral replication cycles in chronic HTLV-1 carriers most likely explains these results [38, 39].

Valproic acid arose as another 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 [40]. 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 [36]. More recently, small open trials of prosultiamine, a vitamin B_1 derivative and known to induce apoptosis in HTLV-1-infected cells [41], and of pentosan polysulfate sodium, an heparinoid with hemorheological properties [42], have provided evidences of some clinical improvement in HAM/TSP. Larger, double-blinded studies are awaited to confirm these results.

Currently, symptomatic treatment employing drugs and physical therapy to alleviate pain—which strongly correlates with a low quality of life of these individuals [43]—spasticity, and bladder control is nowadays the mainstay in the treatment of HAM/TSP.

Conclusions

HTLV-1 causes chronic infection for which there is no cure or neutralizing vaccine. In spite of many advances in the knowledge of the pathomechanisms of HTLV-1, its neuropathogenesis is still poorly understood. It is expected that the development of good animal models in the future may help in a better understanding of the mechanisms involved in the origin of the neurological lesions and, ultimately, in the development of better therapeutic approaches [44].

Compliance with Ethics Guidelines

Conflict of Interest Abelardo Araujo has no disclosures.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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