Neurological Aspects of HIV/Human T Lymphotropic Virus Coinfection

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Abstract

Human T lymphotropic virus type 1 is associated with some neurologic diseases, mainly human T lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis. Human T lymphotropic virus type 2 has also been associated with similar cases of human T lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis, but evidences for a definitive relationship are less clear. On the other hand, neurologic manifestations of HIV infection are quite common, affecting more than one third of patients in HIV clinics. Seroepidemiologic studies show that HIV-infected individuals are at an increased risk for human T lymphotropic virus infection and vice versa in comparison with the general population. Furthermore, HIV/human T lymphotropic virus coinfection has been associated with distinctive immunophenotypes and an increased risk for development of neurodegenerative conditions. Thus, studies on HIV/human T lymphotropic virus coinfection have a practice clinical importance. In this review, we aim to discuss clinical and laboratorial data focusing on neurologic diseases in HIV/human T lymphotropic virus coinfection. (AIDS Rev. 2009;11:71-8)

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Key words

HTLV-1. HAM/TSP. HTLV-2. ATL. HIV. Coinfection.

Introduction

Undoubtedly, the efforts to isolate both human T lymphotropic virus type 1 (HTLV-1)¹ and type 2 (HTLV-2)² enabled the identification of HIV. This fact eventually overshadowed the significance of the discovery of HTLV. Infection with HTLV-1 has a considerable social and economic impact: the infection is endemic in limited-resource areas such as Africa, the Caribbean, and South America. Human T lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)³ is a disabling condition, mostly diagnosed during the most economically productive years of life and is the main neurologic disease caused by this retrovirus. Additionally, other neurologic conditions have also been associated with HTLV-1 infection, which strengthens the concept of the high potential of HTLV-1 to affect the nervous system⁴. Interestingly, in patients with HTLV-1-associated neurologic conditions, the HTLV-1 proviral load is higher than in asymptomatic carriers⁵. This is remarkable because a high proviral load is associated with an increased risk for diseases in HTLV-1-infected patients⁶.

Since the beginning of the HIV epidemic, neurologic disorders have been reported as very frequent and debilitating among AIDS patients⁷. For example, the nervous system is affected in 26-94% of HIV-infected individuals in Brazil⁸, and the same is observed in other countries. Considering that (i) HIV-infected patients are at an increased risk for HTLV infection and vice versa (ii) HIV/HTLV coinfection seems to
increase the risk for neurologic diseases, and (iii) the effects of HAART on HIV/HTLV co-infection are not yet completely understood, reviews about HIV/HTLV co-infection are of utmost importance. Therefore, in the present review we aim to discuss clinical and laboratorial data, focusing on neurologic diseases in HIV/HTLV co-infection.

**Cellular and molecular biology of co-infection: In vitro and in vivo HIV/human T lymphotropic virus interactions**

Both HIV and HTLV share similar genomic organization and encode structural and enzymatic proteins typical to all retroviruses. In addition, their genomes encode accessory proteins that seem to play an important role in viral pathogenesis, such as Tax and Rex in HTLV infection and Tat and Rev in HIV infection. However, the replication strategies used by HIV and HTLV are quite different, which results in distinct outcomes. High levels of virus particles in plasma are observed in HIV infection due to active replication. On the other hand, HTLV-1 is characterized by a poor ability to infect permissive cells as cell-free virions, the chronic infection being maintained mainly by provirus-carrying cell proliferation.

The frequency of HTLV-1/2 infection is unquestionably higher among HIV-infected individuals than in the general population. Furthermore, HIV/HTLV co-infection seems to interfere with the course of the diseases associated with both viruses. In vitro and in vivo evidences indicate that HIV-1 infection is associated with upregulation of HTLV-1/2 expression and a higher risk for diseases. Superinfection of HTLV-1-transformed cell lines with HIV-1 results in an increased HTLV-1 protein expression. Indeed, this enhancement was observed only after infection with active HIV-1 virus, but not following exposure to inactivated viral particles or transfection with the HTLV-1 tat gene. However, the HIV-1 Rev protein was found to enhance HTLV-1 gene expression, acting through the 5'-RU5 portion of the HTLV-1 genome. In addition, peripheral blood mononuclear cells (PBMC) from HIV-1/HTLV-1-coinfected individuals proliferate in vitro at a higher rate than HIV-monoinfected cells. This is similar to the spontaneous proliferation observed with HTLV-1-infected PBMC.

Recently, it has been shown that intercellular contacts drastically enhance HIV transmission and replication compared to what is observed with free virus infection. This finding indicates that cell-to-cell transfer is the predominant mode of HIV spread. The HIV cell-to-cell transfer relies on a rapid recruitment of the cellular interface of CD4, CXCR4, talin, and lymphocyte function-associated antigen 1 on the target cell and of Env and Gag proteins on the HIV-infected effector cell. This explains the highly efficient HIV replication in lymphoid organs, where high amounts of CD4+ T-cell and slow cell movement would facilitate cellular cross talk and viral transmission. As for HIV-1, lymphoid organs are believed to be a major in vivo reservoir for HTLV-1, followed by circulating PBMC. Indeed, HTLV-1 has also been shown to spread through an intracellular reorganization of the viral components near the cell-cell junction. This has been termed "virologic synapse".

Sun, et al. demonstrated that HIV-1-infected cells can fuse with both HTLV-1-expressing cells and latently HTLV-1-infected cells, and the resulting syncytia could function as a "tunnel" by which the Tax protein would diffuse, leading to a more potent induction of HTLV-1 proteins and virions in cells harboring latent HTLV-1 provirus. This HIV-1-dependent transfer of HTLV-1 Tax protein might explain, at least partially, why coinfection with HIV-1 allows HTLV-1 to overcome the strong and chronically activated T-cell response, which could result in the onset of HAM/TSP in a higher proportion of coinfected individuals.

On the other hand, HTLV-2 downregulates HIV-1 replication in interleukin 2 (IL-2)-stimulated primary PBMC of coinfected individuals through the expression of macrophage inflammatory protein (MIP) 1α. The MIP-1α and other CC-chemokines, such as RANTES and MIP-1β, bind to CCR5, a cell surface coreceptor for macrophage-tropic (M-tropic) HIV-1 strains, which is dominant during early AIDS and clinically latent HIV infection. In addition, CXCR4 is the coreceptor of the more cytopathic T-cell-tropic (T-tropic) HIV strains that emerge in later stages of disease. The acquisition of CXCR4 usage as coreceptor corresponds to the switch from M-tropic to T-tropic phenotype, to the loss of sensitivity to the suppressive effects of CC-chemokines, and to a significant decrease in CD4+ T-cell counts. Besides, HTLV-1-specific CD8+ cytotoxic T-lymphocytes derived from patients with HAM/TSP are an important source of MIP-1α and MIP-1β, suggesting that HTLV-1 and -2 may influence HIV replication via chemokine release. Notably, MIP-1α alone seems to account for most of the anti-HIV activity, unlike RANTES and MIP-1β. Moriuchi, et al. also observed...
this same interference using supernatants from HTLV-1-infected cell cultures. In this experiment, replication of M-tropic HIV-1 was inhibited, but replication of T-tropic was enhanced\textsuperscript{39}. Altogether, these findings suggest that HTLV-1 or -2 coinfection in HIV-infected individuals may facilitate transition from an M-tropic to a T-tropic HIV phenotype, which is indicative of progression to an advanced stage of HIV disease. Furthermore, coinfection with T-tropic HIV-1 and HTLV-1 significantly enhanced HIV-1 replication, whereas coinfection with M-tropic HIV-1 enhances HTLV-1 expression\textsuperscript{16,34,35}.

In vivo data show that HIV/HTLV-2-coinfected patients present lower levels of T-cell activation, which reflects the lower rate of HIV replication and correlates with the lower HIV RNA load in plasma compared to HIV-monoinfected patients\textsuperscript{36}. This is in agreement with the lower rate of HIV replication and correlates with the lower HIV RNA load in plasma compared to HIV-monoinfected patients\textsuperscript{36}. In this agreement with the slower rates in the decrease of CD4\textsuperscript{+} T-cell counts in HIV/HTLV-1/2-coinfected patients, resulting, on average, in higher CD4\textsuperscript{+} T-cell counts\textsuperscript{37,38}. Although in vitro and in vivo findings are conflicting at first sight, one should consider the stage of HIV disease. Therefore, whereas HTLV-1/2 may accelerate the progression of HIV disease\textsuperscript{27,33}, the immunomodulatory effect of HTLV-1/2 Tax protein would be a positive stimulus for expansion of T-cells at late stages by increasing the synthesis of IL-2 and interferon gamma (IFN-\gamma) by HTLV-infected cells\textsuperscript{39}. Although higher CD4\textsuperscript{+} T-cell counts in coinfected subjects could potentially delay the progression to AIDS, an increased frequency of clinical complications, such as thrombocytopenia and respiratory and urinary tract infections, is observed. Therefore, it is possible that CD4\textsuperscript{+} T-cell function presents qualitative defects in coinfection subjects, which may render this parameter less useful in the clinical setting.

As discussed below, HIV/HTLV coinfection is associated with a higher risk for neurologic diseases. HAM/TSP is a slowly progressive neurodegenerative disease characterized by perivascular cuffing of mononuclear cells accompanied by parenchymal lymphocytic infiltration. In vitro assays showed that endothelial cells can be productively infected by HTLV-1 and expression of the tight-junction proteins in these cells is altered, which facilitates lymphocyte traffic and blood-brain barrier (BBB) breakdown\textsuperscript{16,34,35}. In situ hybridization also revealed the presence of HTLV-1 RNA in spinal cord and cerebellar sections, and phenotypic analysis demonstrated that at least some of the infected cells were astrocytes\textsuperscript{41}. Mor-Vaknin et al. also showed that BBB breakdown would occur, at least partially, by syncytium formation between the HTLV-1-infected T-cells and astrocytes\textsuperscript{42}. These cells usually respond to trauma, stroke, or neurodegeneration by undergoing cellular hypertrophy. However, it has been demonstrated that, as a consequence of T-cell attack, infected astrocytes undergo polarization, extending a major protrusion towards the immunological synapse formed with effector T-cells, and withdrawing most of their multipolar finer processes\textsuperscript{33}. On the other hand, microglia cells are the main reservoir for HIV-1 in the central nervous system, and multinucleated giant cells, which result from the fusion of HIV-1-infected microglia and brain macrophages, are the hallmark of HIV dementia\textsuperscript{34,35}. Therefore, cells of the monocyte-macrophage lineage are of particular importance in this process due to their ability to cross the BBB and spread HIV-1 infection into the central nervous system (CNS)\textsuperscript{46}. Altogether, these events could contribute to BBB breakdown. Levin, et al. presented the case of a patient with both HAM/TSP and HIV-associated dementia\textsuperscript{47}. Both viruses were detected in the CNS, but HTLV-1 was localized in astrocytes and HIV in the macrophage/microglia, with no coinfection of a single cell phenotype. This suggests that mechanisms other than coinfection of the same CNS cell may play a role in the development of neurologic disease in HIV/HTLV-coinfected patients. Therefore, BBB breakdown related to HIV and/or HTLV infection could accelerate the emergence of neurodegenerative conditions associated with either virus during coinfection.

HIV/human T lymphotropic virus coinfection and human T lymphotropic virus 1/2 proviral load

Although in vitro data suggest that HIV and HTLV could reciprocally enhance their expression, it has been shown that HIV-1 infection does not alter HTLV-1 or HTLV-2 Proviral loads in dually infected individuals in comparison to HTLV-1 or -2 monoinfected subjects. In vivo data do not rule out the in vitro-based hypothesis that HIV-T coinfection would increase the HTLV-3 proviral burden in the PBMC. However, depletion of the CD4\textsuperscript{+} T-cell subset, the main target of HTLV-1, could be counterbalanced by an upregulation of HTLV-1 replication\textsuperscript{48}. Data from HIV/HTLV-2-coinfected subjects under HAART confirmed this event. A transient increase was observed in the HTLV-2 proviral load concomitant to a decrease in HIV-1 viremia. This
would reflect the rapid blocking of HIV-1 replication in response to therapy, causing an increase in the number of circulating T lymphocytes carrying the HTLV-2 proviral DNA. 

An increased HTLV-2 proviral load following HAART may predispose HIV-coinfected patients to HTLV-2-related diseases. This may include conditions such as myelopathy, cutaneous lymphoma, or peripheral neuropathy. Since HTLV-associated diseases usually have a long incubation period, it is probable that the prolonged lifespan of HIV-infected individuals after HAART will allow the observation of more cases of HAM/TSP in the course of HIV/HTLV-1 coinfection.

**Clinical outcomes**

Since HIV and HTLV affect both the peripheral and the central nervous system, there is a reasonable concern about an increased risk for neurologic diseases in coinfection, mainly as a result of upregulated HTLV-1 expression during HIV/HTLV coinfection (see above). Double infection with HIV increases HTLV-1 antigen production, suggesting an upregulation of HTLV-1 replication by HIV. This in vitro observation could explain the increased risk of HAM/TSP during HIV/HTLV-1 coinfection. Levels of HTLV tax and rex mRNA in PBMC in HIV/HTLV-coinfected patients are higher than in HTLV mono-infected individuals.

**Myelopathy**

The most common neurologic manifestation of HTLV-1 is HAM/TSP. This disorder manifests clinically by a slow, progressive spastic paraparesis, neurogenic bladder disturbances, and less evident sensory signs. Development of neurologic disability typically occurs during the first or second year of the disease, indicating a possible initial inflammatory phase followed by a more protracted degenerative stage. An important factor that seems to determine the risk for HAM/TSP and its progression is the HTLV-1 proviral load; patients with high proviral loads are at increased risk for both HAM/TSP development and faster progression of the disability than those with low proviral loads, possibly indicating an increased proliferation or migration of HTLV-1-infected lymphocytes to the CNS. 

Recently, we have demonstrated that not only HAM/TSP patients have higher proviral load than asymptomatic carriers; HTLV-1-infected patients with other associated neurologic disturbances can also exhibit a high proviral load. This strengthens the role of a high HTLV-1 proviral load in the pathogenesis of neurologic diseases.

Approximately 2% of HTLV-1-infected individuals will develop HAM/TSP during the course of infection. Also, HTLV-2 has been associated with similar cases of HAM/TSP, although evidences for a definitive relationship are less clear. On the other hand, HIV infection is classically associated with vacuolar myelopathy, a disease clinically similar but histopathologically distinct from HAM/TSP. Around 10% of AIDS patients used to be affected by vacuolar myelopathy in the pre-HAART era, but nowadays this is rarely diagnosed. However, HIV-infected patients are not free from developing myelopathy, considering that HIV-infected patients are at an increased risk for HTLV-infection and that both viruses seem to interact synergistically in terms of the development of neurologic diseases. Thus, it is not surprising that HIV/HTLV-coinfected patients have a higher probability to develop myelopathy, even in the HAART era.

Berger, et al. were the first to assume that HIV-infection might increase the susceptibility for the development of myelopathy in HIV/HTLV-coinfected patients. In a serological survey for HTLV infection in a cohort of 242 HIV-infected patients, they identified two subjects coinfected by HTLV-1 and two coinfected by HTLV-2. All coinfected patients except one (HIV/HTLV-2) had a myelopathy clinically similar to HAM/TSP. Similar results were described in a Brazilian cohort of HIV/HTLV-1-coinfected patients. Harrison, et al. reported that the frequency of myelopathy was higher in coinfected than in HIV mono-infected patients (11/15 HIV/HTLV-coinfected versus 10/62 HIV mono-infected individuals; OR: 14; p < 0.00004).

More recently, Beilke, et al. described four cases of myelopathy among 41 HIV/HTLV-1-coinfected patients. The prevalence of HTLV infection in their cohort of HIV-infected individuals was 7.4%. The majority of coinfected patients in the Beilke series were infected by HTLV-2 (56.5%), and no cases of myelopathy were described. Different from other reports, Posada-Vergara, et al. described some cases of myelopathy among HIV/HTLV-2-coinfected patients. In a prospective cohort, they identified four out of 37 HIV/HTLV-2-coinfected patients with myelopathy, while none of the 13 HTLV-2 mono-infected patients had neurologic abnormalities.
**Peripheral neuropathy**

Although there have been some controversies regarding the importance of peripheral nerve involvement in HTLV-infected individuals, peripheral neuropathy has been definitely described in association with this virus. Peripheral neuropathy associated with HTLV-1 is characterized by paresthesia, burning sensations, and abnormal superficial sensation distally in a stock and glove distribution and generally coupled with abolished ankle jerks. The greatest difficulty in these cases is to recognize some milder abnormalities in patients with HAM/TSP. A comprehensive history together with a meticulous neurologic examination looking for peripheral nerve dysfunction should lead to a precise diagnosis.

The reported frequency of peripheral neuropathy in HAM/TSP patients varies from negligible to 32%64-66. A few reports have described the occurrence of peripheral neuropathy in HTLV-1-infected individuals without HAM/TSP. In a recent clinical, electrophysiological, and anatomopathological study, peripheral neuropathy was identified in HTLV-1-infected individuals without HAM/TSP: 21 out of 335 patients (6.3%) had clinical and/or electrophysiological abnormalities suggestive of a polyneuropathy67.

The pathogenesis of HTLV-1-related peripheral nerve diseases is presently unknown. Although less restrictive than the BBB, the blood-nerve barrier is also a limiting factor to the entrance of many substances and biological agents into the peripheral nerve microenvironment. The barrier appears to be located at the endoneurial capillaries. It is well known that the blood-nerve barrier is absent at the dorsal root ganglia and in the terminal branches of sensory and motor nerves. The lack of a barrier at these sites may allow the entrance and retrograde transport of neurotoxins or inflammatory substances. This could explain the occurrence of isolated peripheral neuropathy even in the absence of HAM/TSP.

Regarding HIV infection, peripheral neuropathy is one of the most disabling and frequent complications occurring during this infection. Distal sensory polyneuropathy may be secondary to the HIV itself or may be due to the toxicity of some antiretrovirals. The clinical features of both conditions are identical, with pain and paresthesia being the main symptoms68. Before HAART, distal sensory polyneuropathy was clinically diagnosed in about 89%69 of patients. Nowadays, the majority of prospective studies estimate the incidence of peripheral neuropathy to be around 30%-40% with a prevalence of 53%71. Noteworthy, histologic evidence of peripheral neuropathy in autopsy series is close to 100%69.

A higher prevalence of peripheral neuropathy in HIV-HTLV-2 coinfection when compared with HIV monoinfection was reported by some groups, suggesting that HTLV-2 could be a predisposing cofactor to development of peripheral neuropathy in HIV-infected patients. Zeheider, et al. studied 30 HIV/HTLV-2-coinfected patients for 28 months and reported a higher frequency of peripheral neuropathy in this group compared with HIV-monoinfected patients (OR: 3.3; p < 0.009)72. During the period of the study, one patient developed a myelopathy. More recently, in a large cohort followed for many years, Beilke, et al. verified that both HIV/HTLV-1 and HIV/HTLV-2-coinfected patients were more likely to present neurologic complications, including peripheral neuropathy, than HIV-monoinfected individuals73. Harrison, et al. also described that HIV/HTLV-1-coinfected patients had a higher chance of developing peripheral neuropathy than HIV-monoinfected patients. However, this difference was weakened after adjustment for intravenous drug use history61.

**Miscellaneous**

An interesting speculation can be made regarding cognitive dysfunction in HIV/HTLV-coinfected patients. Infection with HIV can result in mild to severe cognitive deficits – the so-called HIV dementia. Undoubtedly, HAART reduced dramatically the incidence of HIV dementia, but a considerable number of patients still exhibit cognitive decline nowadays. This can be explained by the effects of aging, since patients are surviving longer, and by neurodegeneration due to chronic presence of activated microglia. The pathogenesis of HIV dementia is out of the scope of this paper, but readers are referred to a recent review about this subject.

Cognitive dysfunction in HTLV-1 infection has been less studied. The interest for cognitive disturbances in HTLV-1 infection started after an increasing number of reports describing brain abnormalities in the magnetic resonance imaging of HAM/TSP patients74-75. Since white matter lesions of HAM/TSP are in some aspects similar to those observed in patients with multiple sclerosis and in HIV-infected people, cognitive deficits in HAM/TSP patients may also occur. Most of the published papers on cognitive disturbances
in HAM/TSP describe psychomotor slowing, attention deficits, as well as visual and working memory deficits. However, a number of methodologic problems arise from many of these series. For example, extensive batteries for assessing cognitive dysfunction have been used in only three out of the nine published papers76-78, and in only one study a control group was used78. The remaining papers are either case reports79-81, studies on cognitive event-related potentials82, or epidemiologic surveys about the seroprevalence of HTLV-1 in demented patients83,84. Our group demonstrated, through extensive neuropsychological assessment and with a negative control group, that HTLV-1 infection was associated with mild cognitive deficits, characterized by impairments in psychomotor speed, verbal fluency, verbal and visual memory, selective and alternate attention (mental flexibility), and visuconstructive abilities85. Both HAM/TSP patients and asymptomatic carriers had a worse performance in several tests when compared with the control group. The HIV/HTLV coinflection could be associated with a higher risk of neuropsychological dysfunction, but this hypothesis has not been formally assessed so far.

Although antiretroviral therapy has unquestionably changed the natural course of HIV disease, its role in HTLV infection is practically none. Two antiretroviral drugs have been tried in HAM/TSP. Zidovudine inhibited HTLV-1 reverse transcriptase both in vitro and in a rabbit infection model86, but clinical trials in patients with HAM/TSP have shown conflicting results87,88. Lamivudine was reported to reduce HTLV-1 proviral load in five patients, with clinical improvement in one patient with acute HAM/TSP89. Recently, 16 patients were randomized to receive a combination of zidovudine and lamivudine or placebo90. No significant changes were seen between the two arms regarding pain, bladder function, disability score, gait, proviral load, or markers of T-cell activation or proliferation. Failure to detect clinical improvement may reflect irreversible damage to the nervous tissue and lack of virologic effect may indicate inactivity of these nucleoside analogs against the HTLV-1 reverse transcriptase in vivo. Finally, the effects of HAART in coinfected individuals have not been completely studied to date. The best evidences so far come from HIV/HTLV-2-coinfected patients (see above) and show that antiretroviral therapy has an enhancing effect on proviral load91. Nevertheless, there is no evidence that this increase in proviral load is associated with neurologic diseases.

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