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HTLV-1 Associated Neurological Complex. What is Hidden below the Water?

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Abstract

The human T-cell lymphotropic virus type 1 (HTLV-1) infects 5-10 million people worldwide and causes fatal and disabling diseases in a significant proportion of them. A chronic myelitis named HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) is the typical neurological manifestation of HTLV-1. However, other neurological syndromes can be either associated with HAM/TSP or occur in isolation in the HTLV-1 infected individual. Although this fact has been widely described over the years, it has been somewhat neglected by the mainstream literature, which has been largely focused on HAM/TSP. Cognitive dysfunction, encephalopathy, neurogenic bladder, motor neuron disease, inflammatory myopathies, polyneuropathy, and dysautonomia can also occur in the HTLV-1 infected patient and may remain unnoticed to the unsuspecting physician. In the present review, we intend to draw attention, primarily to the infectious disease specialist and to the general practitioner, to the fact that HTLV-1 has a broader neurological spectrum than the designation HAM/TSP suggests and that infected individuals may harbor other neurological syndromes in addition to HAM/TSP. **(AIDS Rev. 2019;21:211-217)**

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Key words

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Introduction

The human t-lymphotropic virus type 1 (HTLV-1) was the first pathogenic human retrovirus to be identified[1]. HTLV-1, including its seven subtypes (HTLV-1a to 1g), is endemic in South America, Japan, Melanesia, sub-Saharan Africa, the Caribbean, Australia, and the Middle East. HTLV-1 is transmitted by sexual contact, breastfeeding or blood transfusions[2].

HTLV-1 infection causes the activation and clonal proliferation of infected T cells, a process for which the viral proteins Tax and HTLV-1 bZIP factor (HBZ) is essential. HTLV-1 is almost entirely cell-associated *in vivo*; cell-free virus particles are usually undetectable, and accidental transmission of HTLV-1 by blood transfusion has only been recorded after the transfusion of cellular blood products. It is estimated that approximately 5-10 million people are infected around

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the world, although most of them remain asymptomatic throughout their lives[2]. HTLV-1 infection is initially asymptomatic, and this stage can last for several years or even decades, after which subsequent inflammatory and malignant diseases usually occur.

HTLV-1 causes an aggressive malignant disease of CD4+ T cells known as adult T cell leukemia/lymphoma (ATLL) in ~ 5% of infected individuals. Approximately 1% of HTLV-1 infected people also develop a chronic inflammatory disease of the central nervous system (CNS), known as HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP)[3].

The identification of prognostic biomarkers and molecules that may be implicated in the pathogenesis of HTLV-1 infection is vital to understanding disease development and progression. The interaction between viral virulence factors and host defense mechanisms seems to be paramount in this regard. The host human leukocyte antigen (HLA) profiles and the HTLV-1 proviral load (PVL) are known as prognostic markers for HTLV-1-associated diseases; however, they are insufficient to determine the HTLV-1 infection outcome. Therefore, other factors may be involved, such as the host neopterine, Tax, and HBZ levels. In a recent study, Tarokhian et al.[4] addressed these specific factors in Iranian patients. They concluded that Tax, HBZ, and PVL were very helpful for monitoring of HTLV-1-infected subjects. Host factors, such as the HLA profile, an important factor to determine the disease outcome in infected individuals from Japan and elsewhere[5,6] were not significantly important in the Iranian population. Plasma neopterin and the PVL could, on the other hand, be used as a reliable biomarker for HAM/TSP monitoring during treatment[4].

HAM/TSP is the most common neurological consequence of HTLV-1 infection, but it is not the only one. Other neurological syndromes can be either associated with HAM/TSP or occur in isolation in the HTLV-1 infected person. Although this fact has been widely described over the years, it has been somewhat neglected by the mainstream literature, which has been largely focused on HAM/TSP. The reason for that is unclear. Maybe many of these other syndromes are oligosymptomatic and go unnoticed to the unsuspecting physician. In addition, because they are not traditionally associated with HTLV-1 specific serologic test, which are not included in the diagnostic routine by the doctor faced with such cases. Geographical variations of prevalence could also explain underreporting in many series published in the literature. Whatever the reason, the fact is that these non-HAM/TSP neurological manifestations of HTLV-1 have been largely neglected by the literature. In the present review, we aim to demonstrate that HTLV-1 has a broader neurological spectrum than the name HAM/TSP suggests and that infected individuals can present with other isolated or hybrid syndromes.

Physicians who deal with HTLV-1 infected patients or with patients who have one of the neurological syndromes described below should remain alert and pursue this etiological association when faced with suspected cases. In other words, as already said by Louis Pasteur (1822-1895): "*La chance ne sourit qu'aux esprits bien préparés*" (*Luck smiles only at well-prepared minds*).

In the following paragraphs, we describe the various clinical conditions that comprise the "*HTLV-1 neurological complex*."

HAM/TSP

HAM/TSP is the classical and most common neurological syndrome associated with HTLV-1. The term HAM/TSP has withstood since 1989, probably due to historical reasons, although this expression is no longer scientifically accurate because this disorder is neither exclusively myelopathy nor strictly a tropical disease[7]. In fact, many studies have demonstrated the widespread nature of the neuropathological lesions in HAM/TSP, which are not restricted to the spinal cord[8,9].

HAM/TSP is a neurological disorder defined by clinical and serological criteria[10] (Table 1). The condition manifests clinically by spastic paraparesis, neurogenic bladder disturbances, and less conspicuous sensory signs, reflecting the predominant involvement of the thoracic spinal cord. Some other clinical variants have been described, such as the one with major cervical cord involvement[11]. These variants should always be remembered in the clinical context of HAM/TSP with atypical neurological presentations.

The mean age of onset of HAM/TSP is 40-50 years and the frequency is higher in women than in men[2]. All the evidences suggest that the host immune response causes the tissue damage observed in the CNS. The interaction between the host immune system and HTLV-1- infected cells regulates the development of the disease. In particular, HTLV-1-specific CD8-positive cytotoxic T lymphocytes (CTL) against HTLV-1 have been thought to play a pivotal role in the development of HAM/TSP. HTLV-1 PVL, which is strongly related to the risk of developing HAM/TSP, remains relatively stable within each subject while HTLV-1 drives a strong

Table 1. Diagnostic criteria for HAM/TSP presented according to the level of ascertainment[10]

Definite
- A non-remitting progressive spastic paraparesis with a sufficiently impaired gait to be perceived by the patient. Sensory symptoms or signs can be present. When present, they remain subtle and without a clear-cut sensory level. Urinary and anal sphincter signs or symptoms can be present
- Presence of HTLV-1 antibodies in serum and CSF confirmed by western blot analysis and/or a positive PCR for HTLV-1 in blood and/or CSF
- Exclusion of other disorders that resemble HAM/TSP

Probable
- Monosymptomatic presentation: spasticity or hyperreflexia in the lower limbs or isolated positive Babinski sign with or without subtle sensory signs or symptoms, or neurogenic bladder only confirmed by urodynamic tests
- Presence of HTLV-1 antibodies in serum and/or CSF confirmed by western blot analysis and/or a positive PCR for HTLV-1 in blood and/or CSF
- Exclusion of other disorders that resemble HAM/TSP

Possible
- Clinical presentation with some or all of the symptoms described above
- Presence of HTLV-1 antibodies in serum and/or CSF confirmed by western blot analysis and/or a positive PCR for HTLV-1 in blood and/or CSF
- Disorders that resemble HAM/TSP have not been excluded

HTLV-1: human t-cell lymphotropic virus type 1, HAM/TSP: HTLV-1 associated myelopathy/tropical spastic paraparesis, CSF: cerebrospinal fluid, PCR: polymerase chain reaction.

proliferation of infected T-cells[3]. It is known that PVL and production of proinflammatory cytokines are increased in patients with HAM/TSP and that these play a role in the pathogenesis of the disease. In asymptomatic carriers, PVL should be measured since it is apparently a good predictor of illness. However, longitudinal studies show that although the PVL tends to be significantly higher at baseline in HAM/TSP their values do not change significantly over time, except for non-significant fluctuation in the same patient[12,13].

HAM/TSP can also be associated with other systemic symptoms such as pulmonary alveolitis, uveitis, arthritis, dermatitis, Sjögren's syndrome, Behçet's disease, thyroid disease, crusted scabies, cystitis, and prostatitis. The coincidence of ATLL and HAM/TSP in the same patient, although relatively rare has been increasingly reported and can impact the prognosis of both diseases[14]. Peripheral neuropathy, myopathy, autonomic failure, and cognitive dysfunction may eventually be associated in patients with HAM/TSP[7].

In large metropolitan areas where human immunodeficiency virus type 1 (HIV-1), hepatitis C virus (HCV), and HTLV-1 viral transmission events occur through sharing of needles and through sexual activities, particularly among men who have sex with men it is not uncommon to find patients with HAM/TSP coinfected with HIV or HCV. Coinfection rates vary with the population studied. Even in endemic countries such as Brazil, HTLV/HIV coinfection rates vary by region, and studies showed prevalences ranging from 2.25% to 21.11%[15], on the other hand, in Spain, a country with low endemicity for HTLV-1, these rates tend to be lower and more uniform (3.2%)[16].

Studies suggest that people living with HIV/acquired immunodeficiency syndrome (AIDS) infected with HTLV-1 are more prone to develop neurological disease and malignancies. In addition, coinfection may mask the diagnosis of human AIDS, since CD4+ T cell counts increase in these individuals[17].

Because the spinal cord is a common target of HIV infection[18], the presence of a chronic progressive myelopathy in an HIV-infected individual usually leads to the clinical suspicion of HIV-related vacuolar myelopathy. In such cases, one should always consider the possibility of an HIV-HTLV-1 coinfection causing HAM/TSP.

The impact of HCV and HTLV-1 coinfection on the natural history of HCV is largely unknown. Because HTLV-1 causes immunological dysfunction, it has been postulated that HCV/HTLV-1 coinfection could increase the rate of disease progression, a higher risk of hepatocellular carcinoma, and a poorer response to antiviral therapy[19]. These assumptions, however, have never been confirmed[19]. Similarly, according to recent findings, HCV does not appear to interfere with the prognosis of patients with HAM/TSP[20].

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[21]. However, the disease may develop faster (from 1 month to a few years), particularly among recipients of transplanted organs from infected donors[22,23].

A more comprehensive review of HAM/TSP can be found elsewhere[3].

HTLV-1-associated cognitive dysfunction

The incidence of white matter lesions in the brain is significantly higher in HAM/TSP than in controls. These lesions affect the deep and subcortical cerebral white matter multifocally, sparing the periventricular regions

and gradually increase in number, as the disability status become worse[9]. These findings coupled with autopsy reports showing brain involvement in HAM/TSP led investigators to search for cognitive dysfunction in HTLV-1 infected individuals.

It is well known that higher levels of inflammatory mediators have been associated with cognitive dysfunction among elderly subjects, patients with autoimmune diseases, chronic hepatitis C, Alzheimer's disease, and depression[24]. Cognitive impairment among HAM/TSP patients was first described by Cartier et al.[25,26] At least 50% of a series of individuals with HAM/TSP who underwent neuropsychological tests had some degree of intellectual and affective impairment. Subsequently Silva et al.[27] demonstrated lower performance in neuropsychological tests not only in patients with HAM/TSP but also in HTLV-1 asymptomatic carriers when compared with controls. There was no relationship between the degree of motor disability and cognitive deficits in the TSP/HAM group. Psychomotor slowing and deficits in verbal and visual memory, attention, and visuomotor abilities characterized the neuropsychological impairment in HTLV-1 infection, pointing to a predominantly subcortical involvement[27]. This raised the hypothesis that HTLV-1 could be, *per se*, responsible for the subcortical cognitive dysfunction.

These patients presented higher levels of peripheral cytokines in parallel with the worst cognitive performance suggesting an inflammatory mechanism involved in the impaired cognitive function. These findings suggest that cognitive impairment in HAM/TSP patients might be linked to the persistent inflammatory activity that is found in the disease[24].

HTLV-1 encephalopathy and encephalitis

Encephalitis and encephalopathy are rare complications of HTLV-1 infection. Since the early nineties Japanese investigators have described both *in vivo* and in necropsy studies the involvement of the brain in HAM/TSP[8,9].

Asymptomatic brain inflammation can be detected in patients with HAM/TSP through advanced imaging techniques such as 11C-PBR28 positron emission tomography coupled with magnetic resonance imaging (MRI) of the brain[28].

Overt encephalitis, although rare, has been described in the literature. Crawshaw et al.[29] have recently reviewed the literature and detected nine cases of overt encephalopathy or encephalomyelopathy associated with HTLV-1. Most of these patients had a previous diagnosis of HAM/TSP before developing encephalopathic features, and the time between the onset of the myelopathy and the encephalopathy ranged from < 4 weeks to 24 years. In all patients with HAM/TSP, a subacute prodromal deterioration in mobility occurred. Five of nine cases had fever or hypothermia at encephalopathy onset. All had altered mental state and reduced conscious level. Four of nine had seizures. Six of nine patients had a cerebrospinal fluid (CSF) pleocytosis, predominantly either with monocytes or lymphocytes. CSF protein was high in six patients. When PVL was measured, this was higher in CSF than in peripheral blood mononuclear cells. When performed, MRI of the brain and electroencephalogram showed various abnormalities, with few consistent features across subjects, though three had reversible white matter changes on MRI. Of seven patients treated with intravenous (IV) corticosteroids, four responded well with resolution of encephalopathy.

It is still a matter of debate if HTLV-1 *per se* should be considered the sole cause of encephalopathy or a predisposing factor increasing the risk of encephalopathy in patients with existing risk factors such as coinfections or autoimmune conditions. If HTLV-1 associated encephalopathy is suspected, IV corticosteroids may be an effective initial treatment option.

HTLV-1 neurogenic bladder

Voiding dysfunction due to neurogenic bladder plays an important role in the constellation of symptoms of HAM/TSP and is one of the most frequent complaints in these patients[3,7,10]. The most common urinary symptoms in HAM/TSP are nocturia (81.4%), involuntary loss of urine (76.9%), urgency (74.4%), increased frequency (60.5%), and dysuria (39.5%). These symptoms have a great negative impact on the quality of life of 81% patients[30]. Detrusor overactivity and bladder-sphincter dyssynergia are the most frequent urodynamic findings in these individuals[30].

One very important aspect of the urinary symptoms in HAM/TSP is that they may precede other motor and sensory signs and symptoms by several months or even years[30,31]. Therefore, patients may present to their primary care physician, gynecologist, or urologist with vague voiding complaints and not being promptly diagnosed if the doctor is not aware of this association.

HTLV-1 can also cause an isolated neurogenic bladder, not accompanying HAM/TSP[32,33]. Silva et al.[33] described neurogenic bladder dysfunction in 4.3% of HTLV-1-infected individuals who did not fulfill the diagnostic criteria for

HAM/TSP. They showed that the HTLV-1 PVL in these individuals was significantly higher than the loads in asymptomatic carriers of the virus being similar to loads of patients with HAM/TSP. These individuals had urinary symptoms for many months before having their serologic status unveiled – median length 61.4 months (range, 42-114 months). Urodynamic studies disclosed mainly underactive detrusor and detrusor sphincter dyssynergia. The median PVL in the neurogenic bladder group was 8 times higher than in the asymptomatic carrier group. This group of patients was followed-up for 10 years. After this period 22% fulfilled clinical criteria for HAM/TSP, while 78% remained with urinary symptoms only (isolated HTLV-1 neurogenic bladder)[31].

The pathogenesis of the neurogenic bladder associated with HTLV-1 is still speculative. The main muscle involved in this condition is the detrusor muscle. Detrusor is a smooth muscle found in the wall of the bladder. It remains relaxed to allow the bladder to store urine and contracts during urination to release urine. It receives motor innervations from cells of the intermediolateral columns of the gray matter from the second to the fourth sacral segments of the spinal cord (the detrusor center). Inflammatory lesions in the lateral columns along the thoracic and lumbosacral segments of the spinal cord could be responsible for both the urinary dysfunction and the pyramidal syndrome seen in patients with HAM/TSP. Theoretically, a discrete inflammatory reaction induced by HTLV-1 infection and restricted to sacral segments could be the cause of isolated bladder dysfunction without the pyramidal syndrome typically observed in patients with HAM/TSP.

HTLV-1 amyotrophic lateral sclerosis (ALS)-like syndrome

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. Since the 1970s, it has been proposed that retroviruses may play a role in its pathogenesis.

Since the description of HAM/TSP in the mid-1980s, at least 35 cases of ALS-like syndrome have been reported. These cases have been summarized elsewhere[34]. Cases of HAM/TSP with ALS-like finding differed from classical ALS by the presence of atypical symptoms of ALS such as sensory and autonomic signs, the long survival of 10.6 years on average, and the response to steroids in many cases[35].

HTLV-1 myopathy

Idiopathic inflammatory myopathies are characterized by skeletal muscle weakness, myalgia, and inflammation, leading to a loss of mobility and increased morbidity. Clinical and histopathological features define three different types of myositis: polymyositis (PM), dermatomyositis, and inclusion body myositis (IBM).

HTLV-1 has been associated with muscle inflammation for many years[36,37]. The two clinical myopathic presentations that have been more frequently described with HTLV-1 are PM and IBM. These myopathies can present either in isolation[38-40] or in association with HAM/TSP[38,39,41,42].

In one study of 38 adult Jamaican patients with PM, 63% were HTLV-1 positive versus 37% seronegative. There was no significant difference between the two serological groups in muscle enzyme levels, antinuclear antibody positivity, or frequency of anti-Jo-1 antibodies. However, the HTLV-1 subgroup of PM had a more insidious presentation and a poorer response to corticosteroid therapy[37].

In Japan Matsuura et al.[40] described a higher prevalence of HTLV-1 (52.3%) among IBM patients in comparison with the general population (11.6%), suggesting a non-coincidental finding. There were no clinical or pathologic differences between HTLV-1 seropositive and seronegative IBM cases. None of the HTLV-1 seropositive patients had clinical features of HAM/TSP but had a high PVL in the peripheral blood. As in PM associated with HTLV-1, these cases also had a poor response to steroids.

The immunopathogenic mechanism behind the association between HTLV-1 and inflammatory myopathies is not as clear as in HAM/TSP. HTLV-1 proviral DNA and viral antigens have been detected in infiltrating mononuclear cells, but not in muscle fibers[43]. Therefore, it has been suggested that myositis in patients with HTLV-I infection is not caused by a direct viral effect, but rather by an immune reaction between HTLV-1 infected CD4+ cells and HTLV-1 specific CD8+ CTLs. Ozden et al.[42] in a report of IBM in a patient with TSP/HAM confirmed the presence of integrated HTLV-1 proviral DNA and viral mRNA transcript in the pathologic lesions of the muscle. They demonstrated the presence of both HTLV-I/infected CD4+ cells and CD8+ T cells directed to the dominant Tax antigen in muscle biopsies. These findings suggest that Tax-specific CTLs are chronically recruited within the muscles of these IBM patients and that an immune interaction between HTLV-1 infected CD4+ cells and

HTLV-1 specific CD8+ CTLs may be involved in the development of both HAM/TSP and IBM.

HTLV-1 peripheral neuropathy

Likewise, in HTLV-1 myopathy, polyneuropathy can be found in HTLV-1 seropositive patients as an isolated manifestation[44,45] or in association with HAM/TSP[44,46].

In HTLV-1 infected individuals without HAM/TSP polyneuropathy was found in 6.3% of infected individuals[45]. The clinical picture is variable, with mainly sensory symptoms predominating in the lower limbs. Patients exhibit variable degrees of distal hypoesthesia, dysesthesia or paresthesia, loss of vibration sense, autonomic symptoms, and associated with abolished or diminished ankle jerks. The knee jerks are more frequently spared, although they can be also diminished or abolished. In the absence of concomitant HAM/TSP patients do not demonstrate any sign of weakness. Electrophysiological studies reveal a pattern of sensorimotor mixed or predominantly axonal polyneuropathy[44,45]. Sural nerve biopsy shows inflammatory infiltrates, axonal degeneration, and segmental demyelination[45] suggesting an immune-mediated mechanism.

The real mechanisms behind HTLV-1 polyneuropathy remain speculative. The topography of the inflammatory process could be distal or proximal to the spinal nerve roots[46]. Some additional clues supporting the immunological nature of the HTLV-1 associated polyneuropathy came from the work of Sawa et al.[47] who described a polyneuropathy running in four members of the same family, all of them infected by HTLV-1. None of them had HAM/TSP. These individuals developed a chronic demyelinating polyneuropathy characterized by mild painful sensorimotor disturbances with distal atrophy of the limbs. Electrophysiological studies were consistent with demyelination of motor fibers. Sural nerve biopsy revealed decreased myelinated fibers, globules and myelin ovoid formation, presence of remyelinated fibers, and infiltration of CD68-positive macrophages with occasional CD4+ T cells inside the nerve fascicles. The polyneuropathy was responsive to steroids. These findings, as a whole, supported an immune-mediated polyneuropathy elicited by the virus in a genetically predisposed population.

HTLV-1 dysautonomia

Autonomic disturbances have been always associated with HAM/TSP and so far have never been described as an isolated phenomenon[48-51]. It is characterized by impairment of cardiovascular and sweat control indicating a major dysfunction of the sympathetic nervous system. Anatomically, the sympathetic efferents involved in cardiovascular autonomic dysfunction are known to pass through the nucleus intermediolateralis in T1-T4 segments[51]. Taken together, these observations suggest that the thoracic spinal cord injury frequently observed in HAM/TSP leads to autonomic dysfunction.

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. Viral and pathogenesis studies of autonomic tissues are lacking and deserve further investigation.

Conclusion

The clinical spectrum of the neurological manifestations of HTLV-1 is broader than the designation HAM/TSP suggests. The virus can affect other areas of the central and peripheral nervous systems. Particularly in endemic areas, or in individuals from endemic regions, HTLV-1 serology should be requested in patients with the following conditions: progressive chronic paraparesis of undetermined etiology, bladder dysfunction – particularly with neurogenic bladder – predominantly sensory polyneuropathies of obscure origin, inflammatory myopathies, autoimmune encephalomyelitis, slowly progressive, and subcortical cognitive deficits.

In patients with a diagnosis already established of HAM/TSP, a diagnosis of HTLV-1 associated neurological complex[7] rather than “pure” HAM/TSP should be suspected in patients with either severe upper limb weakness, subcortical cognitive deficits not explained by a depressive illness, seizures, altered level of consciousness and meningeal signs, muscle fasciculations and amyotrophy, increased creatine kinase levels coupled with new-onset proximal muscle weakness, distal sensory signs and symptoms in a stock and glove distribution, and abolished ankle jerks or disproportionate diminished ankle jerks in relation to the knee jerks, and autonomic syndromes such as orthostatic hypotension.

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