Epidemiology, Treatment, and Prevention of Human T-Cell Leukemia Virus Type 1-Associated Diseases

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INTRODUCTION

The discovery of the first human retrovirus proceeded rather independently in Japan and the United States. In 1980, Poiesz et al. (83) identified human T-cell leukemia virus (HTLV) in a T-cell line from a patient with cutaneous T-cell lymphoma. Independently, in 1982, Yoshida et al. (103) identified adult T-cell leukemia virus (ATLV). Soon, HTLV and ATLV were shown to be identical at the sequence level and were named HTLV type 1 (HTLV-1) (27).

After the discovery of HTLV-1, a second human retrovirus, HTLV-2, was described. Prevalent in Central and West Africa; in native Amerindian populations in North, Central, and South America; and among cohorts of intravenous drug users in the United States and Europe, HTLV-2 has a similar genome structure and shares approximately 70% nucleotide sequence homology with HTLV-1 (53). In 2005, two more related viruses, HTLV-3 and HTLV-4, were reported in central Africa (49). However, only HTLV-1 has been convincingly linked to human diseases at present.

HTLV-1 has six reported subtypes (subtypes A to F). Diverse studies have been performed on HTLV-1 subtyping but present a minor role in the epidemiological status of the virus. The great majority of infections are caused by the cosmopolitan subtype A, and there is no report of subtype influence on the pathogenic potential of HTLV-1 (24).

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Approximately 20 million people worldwide are estimated to be infected with HTLV-1 (21). Approximately 90% of the infected individuals remain asymptomatic carriers during their lives. In reality, the immunopathogenesis of this retrovirus is intriguing, since its lifelong persistence in CD4$^+$ lymphocytes determines a prolonged interaction between the virus and the immune system, which may result in the broad spectrum of diseases associated with HTLV-1. This may be related to the direct action of the virus on the immune system or a consequence of the response of the immune system to the virus. Since 1986, HTLV-1 screening has been developed and was slowly implemented worldwide (34). In 1993, HTLV-1 screening of blood donors was already performed in all developed countries and in many developing countries where HTLV-1 is endemic. Moreover, hemovigilance studies were performed, where patients who received blood from HTLV-positive donors, transfused before screening was performed or from repeat donors who presented seroconversion to HTLV, were traced and tested for the virus (70).

TRANSMISSION

The most important routes of HTLV-1 transmission were found to be from mother to child and predominantly through breastfeeding, sexual intercourse, and blood contact, including the transfusion of infected cellular products or sharing of needles and syringes (84). The efficiency of the mother-to-child transmission route is estimated to be 20% and has been correlated with individual variables such as HTLV-1 proviral load, the concordance of HLA class I type between mother and child, and the duration of breastfeeding (5). Mother-to-child transmission during the intrauterine period or peripartum has been reported to occur in fewer than 5% of cases (26).

Similarly to other sexually transmitted infections, sexual transmission of HTLV-1 is associated with unprotected sex, multiple sexual partners, lifetime contact with an HTLV-1-infected partner, the presence of genital sores or ulcers, and paying or receiving money for sex (65).

Intravenous exposure to blood is the most efficient mode of HTLV-1 transmission. In the past, this occurred mainly through the transfusion of blood not tested for HTLV-1. Most epidemiological studies of HTLV-1 reported transfusion as an important risk factor for HTLV-1 seropositivity (65). The highest risk is associated with the transfusion of packed red cells (92). Plasma products and cold storage of blood lower the risk of transmission, presumably due to the death of HTLV-1-infected lymphocytes (22). The results from hemovigilance and look-back studies presented additional evidence correlating the transmission of HTLV with cellular blood components (70).

The route of infection has been shown to be related to the development of specific diseases associated with HTLV-1. Adult T-cell leukemia/lymphoma (ATL) has been associated with breastfeeding (26, 98), and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) has been associated with blood transfusion (79). Cases of posttransfusion ATL are exceptional.

GEOGRAPHIC DISTRIBUTION

The geographic distribution of the virus has been studied in the almost 30 years since its initial description, with Japan, Africa, the Caribbean islands, and Central and South America emerging as the areas of highest prevalence in the world (84). When interpreting and comparing data from international prevalence studies, caution must be taken in the population selection criteria, because any difference in the diagnostic strategies can interfere with the final result. The estimation of the global prevalence of HTLV-1 is based mainly on the serological screening of healthy blood donors, which might underestimate the prevalence in the population. The geographic distribution of HTLV-1 infection is shown in Fig. 1. The HTLV-1 prevalence rates have been stratified into high (more than 5% of the population tested), middle (5% to 1%), and low (less than 1%) prevalences (84). The geographic distribution of HTLV-1 infection has intriguing aspects. Areas of extremely high prevalence, clusters of HTLV-1, are surrounded by areas of middle or low prevalence. The clusters predominate in a same-latitude trend (Fig. 1). Phylogeny and molecular epidemiology studies have been used to explain this behavior of the infection (24).

Japan is the most important area where HTLV-1 is endemic. The estimated prevalence in the general population varies from areas in which the virus is not found to selected areas with seroprevalences of up to 37%, such as the southwestern isles of Shikoku, Kyushu, and Okinawa (103). High rates of HTLV-1 infection have been reported for some Caribbean islands in studies of blood donors or segments of the general population. In Jamaica, the prevalence is around 5% (64). In Africa, the seroprevalence increases from the north to the south, varying from 0.6% in Morocco to greater than 5% in several sub-Saharan African countries, for example, Benin, Cameroon, and Guinea-Bissau (23), but more studies of the region are needed. In Europe and North America, the prevalence is low and limited to groups that emigrated from areas of endemicity (64). For blood donors, very low rates were found in France (0.0039%) (17) and the United States (0.025%) (64). In South America, the virus was found in all countries, but more studies of the general population are needed to ascertain the real prevalence of HTLV-1. Medium prevalence was found in blood donors from Chile (0.73%) and Argentina (0.07%) (99). In Brazil, Colombia, and Peru, the prevalences vary considerably according to the area and have been correlated with latitude and altitude in some countries. In Brazil, the highest prevalence was described for the central area and the coast (1.35%), with low prevalences in the north and south (0.08%) (28). In Colombia, a prevalence of 4.3% was reported for the low-altitude areas and a prevalence of 0.73% was reported for the high-altitude areas (50). In Australia, even though the prevalence in blood donors is low, a cluster among Aborigines in the Northern Territory was described, with a prevalence of 14% (4).

SCREENING TESTS AND RESIDUAL RISK OF TRANSFUSION-TRANSMITTED HTLV-1

HTLV-1 screening tests are usually an enzyme-linked immunoassay (EIA) or particle agglutination (PA) assays. EIAs
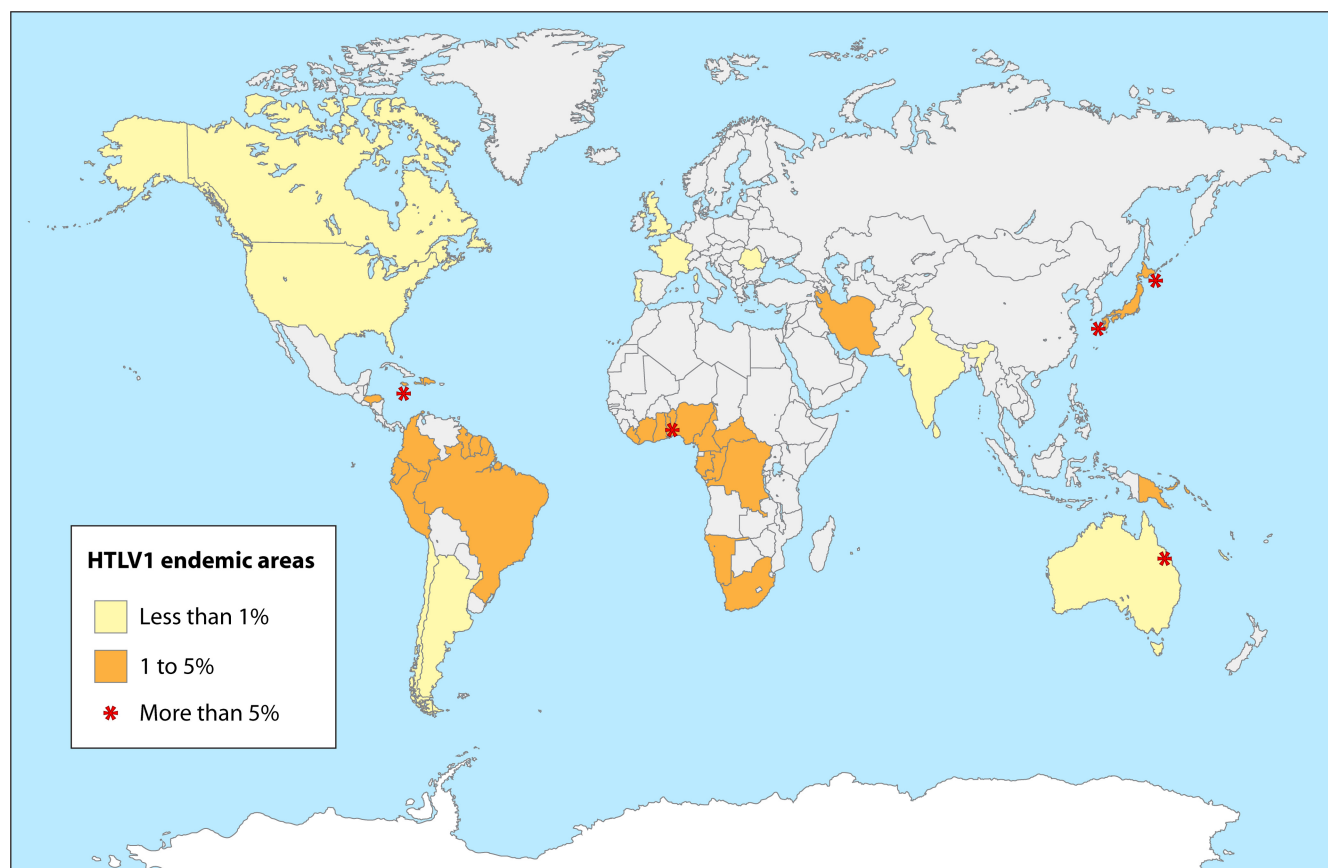
FIG. 1. Geographic distribution of HTLV-1 in countries where the disease is endemic. The stars emphasize high-prevalence areas. The country boundaries shown in the map are not coincidental with the areas of endemicity, reflecting the cluster nature of HTLV infection. (Adapted from reference 84.)

combine testing for HTLV-1 and HTLV-2, while PA assays test only for HTLV-1. Therefore, the chosen technique takes into account the type of retrovirus found in the geographic area. For example, in Japan, where HTLV-2 is not usually found, PA assays are preferred. In Brazil, where both HTLV-1 and HTLV-2 are prevalent, an EIA is used (70). The confirmation is done by testing of the blood with another method that also discriminates between HTLV-1 and HTLV-2. The most commonly used tests are Western blotting (WB), immunofluorescence assay (IFA), or radioimmunoprecipitation assay (RIPA). Indeterminate results of the confirmatory test may occur. The most commonly reported reasons for indeterminate results are the window period, the presence of a viral variant, and an unspecific reaction of the patient's serum to viral antigens (70). PCR, which detects HTLV-1 proviral DNA, has been used for clarifying indeterminate results and also as a confirmatory test. When combined with proviral DNA sequencing or restriction fragment length polymorphism (RFLP) analysis, PCR may also be used for the subtyping of the virus (84). The exclusion of seropositive individuals from the pool of blood donors has resulted in a reduction in the numbers of recipients of contaminated transfusions and in the number of new infections in the overall population (79).

A program to prevent the transmission of HTLV-1 by blood transfusion through the implementation of anti-HTLV-1 screening of donated blood by the PA method was instituted in Japan in 1986 (34). Consecutively, the Centers for Disease Control and Prevention recommended anti-HTLV-1 screening in the United States in 1988 (13). In Canada, the Caribbean, and the French Isles, anti-HTLV-1 screening started in 1989 (15). Continental France started screening in 1991 (17). In Brazil and Australia, blood screening for HTLV-1 was initiated in 1993 (70, 88). In Demark, screening was started in 1994; Portugal and Greece followed soon afterwards (17). In areas of low prevalence, questions remain concerning the cost-benefit of performing blood donor screening for HTLV. In 1995, Sweden decided to screen only the first blood donation for anti-HTLV-1 (97) due to the almost nonexistent local transmission of the virus. Wales and Scotland decided to use minipools (mixture of plasma from blood donors) in 2002 (19).

The risk of HTLV-1 transmission by transfusion varies with the prevalence of this virus in the general population as well as in blood donors. The time interval before seroconversion is also another important variable that interferes with the calculation of the residual risk of transmission. In the case of transfusion-transmitted HTLV-1, the window period usually varies between 41 and 65 days but could be longer (74). The type of blood product is another variable that influences transmission. Plasma and industrial blood products (albumin, immunoglobulin, and antihemophilic factors) do not transmit HTLV-1

TABLE 1. Correlation between HTLV-1-associated diseases and the most common reported clinical manifestations

Common association(s) (reference[s])	Manifestation in HTLV-associated disease			
	HAM/TSP	ATL	HAU	Asymptomatic carrier
Neurological (2)	Polyneuropathy		HAM/TSP	Polineuropathy
Dermatological (6, 7, 8, 29, 45, 51, 60, 71, 76)	Infective dermatitis, acquired Ichthyosis	Infective dermatitis, crusted scabies		Acquired ichthyosis, dermatophytosis
Ophthalmological (59, 61, 69, 81, 82)	Uveitis[a]		Uveitis, conjunctivitis sicca	
Urological (77)	Urinary incontinency, sexual disturbances			
Rheumatologic (18, 35, 37, 40, 56, 57, 82)	Polymyositis, thyroiditis, Sjögren's syndrome, artropathy		Sjögren's syndrome	Polymyositis, fibromyalgia
Pulmonary (40)	Pneumopathy			
Psychiatric (91)	Depression	Depression		
Infections (7, 8)		*Strongyloides stercoralis*, crusted scabies, tuberculosis, leprosy		

[a] See reference 58.

(22). Transmission related to packed red cells and platelets varies according to the period of storage, being the greatest in the first 14 days (92).

The residual risk of transfusion-transmitted HTLV-1 in low-prevalence countries is minimal. In the United States, the estimated risk was 1 out of 921,000 transfusions between 1999 and 2004 (90). In France, the estimated risk was 1 out of 345,000 transfusions between 1996 and 1998 (17). in Canada and Australia between 2000 and 2003, the estimated residual risk was 1 in 1,000,000 (88). In these countries, look-back studies of HTLV-1 and -2 had a very low yield, and their public health benefit is questionable. Conversely, in areas where HTLV-1 is endemic, the residual risk is greater, and the importance of look-back studies and continued monitoring through hemovigilance should be considered due to the higher transmission rates and, therefore, seroconversions in repeat blood donors (10, 70).

IMMUNOPATHOGENESIS

After transmission, reverse transcriptase generates proviral DNA from genomic viral RNA, and the provirus is integrated into the host genome by viral integrase. Afterwards, HTLV-1 infection is thought to spread only through dividing cells, with minimal particle production. Therefore, the quantification of provirus reflects the number of HTLV-1-infected cells, which defines the proviral load. In this regard, an increase in numbers of HTLV-1-infected cells using cell division, by actions of accessory viral genes, especially *tax*, may provide an enhancement of infectivity (94). *tax* expression induces proliferation, inhibits the apoptosis of HTLV-1-infected cells and, conversely, evokes the host immune response, including cytotoxic T cells, to kill virus-infected cells.

In ATL, the *tax* gene plays a central role in the proliferation and transformation of HTLV-1-infected cells *in vivo* (54). Another gene recently described, the HTLV-1 bZIP factor (HBZ), uniformly expressed in ATL cells, seems to have a more important functional role in cellular transformation and leukemogenesis than does *tax* (55). HBZ transcription seems to be correlated with provirus load and also with the severity of HAM/TSP (86).

In HAM/TSP, a proinflammatory microenvironment is the hallmark of the immunological profile (31). The cytokine pattern in the peripheral blood from HTVL-1-infected individuals has been evaluated by using *in vitro* short-term leukocyte incubation and was shown to present distinct clinical grades. It was observed that HAM/TSP individuals display a high frequency of tumor necrosis factor alpha-positive (TNF-α^+) neutrophils and an increased frequency of CD8$^+$ gamma interferon-positive (IFN-γ^+) and CD8$^+$ TNF-α^+ cells, confirming the inflammatory microenvironment related to HAM/TSP progression (9).

HTLV-1-ASSOCIATED DISEASES

The association of HTLV-1 infection with ATL, HAM/TSP, and HTLV-associated uveitis (HAU) has been established (84).

HTLV-1 infection causes subclinical immune suppression that can result in an elevated rate of opportunistic coinfections such as tuberculosis and strongyloidiasis, among others (3). Previous studies have described that arthritis, urinary tract disorders, fibromyalgia, and major depression are frequently found in HTLV-1-infected populations (18, 63, 77, 91). Possibly, some of these diseases either share a pathological mechanism with HTLV-1-related diseases or are related to psychological distress due to the infection. Table 1 summarizes the most common clinical entities associated with HTLV-1.

Adult T-Cell Leukemia/Lymphoma

ATL is an aggressive lymphoproliferative malignancy of peripheral T cells, with short survival in its acute form and an incidence of less than 5% in HTLV-1-infected people (89). It was initially described in Japan and later in the Caribbean region and South America (98). In Europe and the United States, ATL was diagnosed in immigrants from regions of endemicity. Its occurrence is associated with vertical transmission through breastfeeding (26).

ATL occurs more commonly in adults at least 20 to 30 years after the onset of HTLV-1 infection and is more common in males, and individuals infected in childhood may be at a higher

TABLE 2. Adult T-cell leukemia/lymphoma subtypes and diagnosis criteria

Parameter[a]	Criterion for ATL subtype			
	Smoldering	Chronic	Lymphoma	Acute
Lymphocyte count (10^9 lymphocytes/liter)	Less than 4	4 or more[d]	Less than 4	More than 4
% atypical lymphocytes	5 or more	5 or more	1 or less	More than 5
LDH level	1.5× normal upper limit	2× normal upper limit	—[b]	—[b]
Calcium level (mmol/liter)	Less than 2.74	less than 2.74	—[b]	More than 2.74[b]
Presence of:				
Lymphadenopathy	No	No	Atypical lymphocyte in histological analysis	—[b]
Skin lesions	—[c]	—[b]	—[b]	—[b]
Pulmonary lesions	—[c]	—[b]	—[b]	—[b]
Liver lesions	No	—[b]	—[b]	—[b]
Spleen lesions	No	—[b]	—[b]	—[b]
CNS lesions	No	No	—[b]	—[b]
Bone lesions	No	No	—[b]	—[b]
Ascites	No	No	—[b]	—[b]
Pleural effusion	No	No	—[b]	—[b]
Gastrointestinal tract lesions	No	No	—[b]	—[b]

[a] See reference 89.
[b] Not essential.
[c] Not essential; cases of atypical lymphocytes are fewer than 5%; other items have to be completed, and histological analysis of a lesion has to confirm malignancy.
[d] Lymphocytosis, T-cell count of 3.5×10^9 cells/liter or more.

risk of developing ATL (80, 89). In Japan, the fifth decade of life is predominant for the occurrence of ATL (89), and the occurrence of ATL in the fourth decade predominates in Brazil and in Jamaica (84). Possibly, local factors play a role in disease pathogenesis.

Classification. ATL is a heterogeneous disease clinically divided into four subtypes (89). The diagnostic criteria are described in Table 2. The diagnosis of ATL requires the detection of ATL cells in peripheral blood of patients with the acute, chronic, or smoldering type with leukemic manifestations. Typical ATL cells have convoluted nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm. These cells are called flower cells and are considered characteristic of ATL (96). Analysis of CD3, CD4, CD7, CD8, and CD25 is required for an immunophenotypic diagnosis. In the case of the lymphoma subtype, an excisional biopsy of the lymph node is recommended. Samples should be obtained both for histopathological examination concerning malignancy and for molecular analyses in order to evaluate provirus integration into the tissue (96).

The rate of survival varies depending on the subtype: 4 to 6 months for the acute type, 9 to 10 months for the lymphomatous type, 17 to 24 months for the chronic type, and 34 months to more than 5 years for the smoldering type (89).

Clinical characteristics and diagnosis. In the most aggressive forms (acute and lymphomatous types), half of the patients show adynamia; lymphoadenomegalia; hepatosplenomegalia; skin, bone, and multiple visceral lesions or pulmonary infiltration; and hypercalcemia (Table 1).

In the lymphomatous form, superficial or deep lymph node chains are involved.

In the smoldering or chronic form, the symptoms are unspecific; there is no tumor mass involvement, and the skin alterations are predominant, with papulae, plaques, tumor, or long-time erythroderma (89). Strongyloidiasis is frequently associated with all forms (96).

The diagnostic criteria for ATL include the detection of antibodies against HTLV-1 in the peripheral blood of a patient with T-cell lymphoma or leukemia, the presence of hypercalcemia, and, in cases of tumor, monoclonal insertion of HTLV-1 proviral DNA into the tumor cells (Table 1). Skin lesions, high leukocyte counts, and CD25^{+} cells may be present or absent. When the diagnosis of ATL is not done by peripheral blood examination or when a new lesion appears during the monitoring of indolent ATL, biopsy of suspicious lesions should be considered. Frequently involved tissues include lymph nodes, skin, liver, spleen, lung, gastrointestinal tract, bone marrow, bone, and the central nervous system (CNS) (96).

Treatment and prognosis. Despite advances in the support and development of novel treatment agents, the prognosis for ATL remains poor. The variety of therapeutic approaches tested over the past 2 decades is immense. Patients with aggressive ATL have a poor prognosis because of the multidrug resistance of malignant cells, a large tumor burden with multiorgan failure, hypercalcemia, and/or frequent infectious complications as a result of a profound T-cell immunodeficiency (94). A combination of arsenic trioxide, zidovudine, and alpha interferon achieved an impressive remission rate with moderate toxicity (38). The treatment strategy has to be based on the clinical subclassification of ATL and prognostic factors, including watchful expectant approach, chemotherapy, antiviral therapy, and allogeneic hematopoietic stem cell transplantation (94, 96). The major prognostic factors are advanced performance status, high calcium or lactic dehydrogenase (LDH) levels, age of more than 40 years, and more than three involved lesions. Bone marrow involvement is an independent poor prognostic factor for ATL (96). Previous reports have suggested that high doses of corticosteroids in patients with smol-

dering ATL without concomitant antiretroviral therapy might increase the risk of acute ATL (30).

HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis

HAM/TSP is a chronic meningomyelitis of the gray and white matter in the spinal cord, with perivascular demyelination and axonal degeneration (16). Patients will develop a slowly progressive spastic paraparesis, without remissions, with high impairment of gait, autonomic dysfunction of bladder and bowel, and profound repercussions on their abilities and quality of life. Women are affected more frequently than men, and the disease onset occurs in adulthood at an average age of 40 years (78).

The lesion in the CNS caused by HTLV-1 is associated with dense infiltrates of mononuclear cells, largely the CD8$^+$ lymphocyte response (3). Thus, HAM/TSP is considered an inflammatory disease in which cellular damage leads to demyelination (3, 31). Early in the disease, leptomeninges, blood vessels, and parenchyma are infiltrated by CD4$^+$ and CD8 lymphocytes, B lymphocytes, and foamy macrophages. In the chronic phase, the cord infiltrate consists predominantly of CD8$^+$ lymphocytes. The entire spinal cord can be affected, although the lower thoracic level is predominantly affected (20).

Clinical characteristics and diagnosis. The first symptoms are weakness of the lower limbs and lumbar pain, although the initial complaint can be sensory, such as tingling, burning, or pins and needles. In many patients, urinary and sexual problems can be the first symptoms (20, 78). Dizziness is common in the early phase, preceding abnormalities upon a neurological exam, and would be related to a functional disturbance in the vestibule-spinal and motor tracts (25).

The weakness in the lower limbs is associated with moderate to severe spasticity, Babinski's sign, and hyperreflexia. The sensory impairment is mild, the vibratory sense is frequently impaired, and the proprioception is less affected. In the upper limbs, there is also hyperreflexia, usually without muscle weakness. With disease progression, the weakness and the spasticity increase, and the gait becomes worse (66). Urinary and sexual dysfunction are common (77).

Spasticity is a serious problem. It occurs due to a velocity-dependent increase in the muscle tone in response to passive movement and plays a major role in the progression of disability (39). When the spinal cord is deprived of supraspinal control, the motor neuron activity is manifested as muscular spasms. The elevated muscle tone can cause pain, joint contractures, and impaired function. No treatment for spasticity is considered to be effective. Pharmacological management is used to alleviate symptoms (baclofen, diazepam, and tizanidine, etc.). With the evolution of HAM/TSP, the patient goes from a domiciliary walk to a wheelchair (39).

This spinal cord syndrome in HTLV-1 infection affects the autonomic function of the bladder and bowel (14, 63). The patients usually experience frequency, urgency, or urge-incontinence and an elevated postvoid urinary residue (77). The voiding dysfunction, according to the usual level of injury and urodynamic parameters, is an upper motor neuron lesion, with hyperreflexic bladder. There is an overactivity of the detrusor muscle and a dyssynergy of the bladder-sphincter, resulting in an impaired communication between the sacral and the brainstem micturition centers (63, 77).

Urinary tract infections are common and are complicated by lithiasis, vesicoureteral reflux, chronic pyelonephritis, and chronic renal failure. The best bladder management is intermittent cleaning catheterization associated with an anticholinergic drug for the detrusor hyperactivity and an antispastic muscle agent for the external sphincter dysfunction (12, 77).

Constipation is a very common bowel dysfunction. An effective bowel management regimen must take into consideration diet, adequate and timely fluid intake, and pharmacological agents in case of necessity (14).

Neuropathic pain is common in the advanced stage of myelopathy. Dysesthesia is chronic and debilitating pain. It can be affected by the weather, stress, anxiety, or visceral or musculoskeletal stimulus. For many patients, the urinary incontinence or the lumbar pain may be more disabling than the leg weakness (48).

The diagnosis requires the demonstration of HTLV-1 infection and the exclusion of other causes of myelopathy. The accuracy of the diagnosis has improved with neurophysiological tests (1, 25) and with magnetic resonance imaging (MRI) (41). In the early stages of the disease, the neuroimaging of the spinal cord does not define myelopathy, although patients have signals and symptoms of upper motor neuron disease (62). In this phase, functional abnormalities of the spinal cord can be demonstrated through neurophysiological tests (25). The strategies utilized to reach an early and precise diagnosis have epidemiological and therapeutic implications, allowing better counseling and treatment options.

HAM/TSP has a subclinical phase in which the inflammatory lesions are already present but the infected patient presents mild or no neurological abnormalities (16, 25, 46, 62). Vestibular evoked myogenic potentials have been used for testing the vestibule-spinal motor tract and have shown abnormal responses in HTLV-1 carriers with a functional spine otherwise considered asymptomatic (25). In the advanced stage of HAM/TSP, spinal cord atrophy, particularly of the thoracic level, has been reported (Fig. 2).

Brain MRI shows periventricular and subcortical white matter alterations. The high signal intensity and the contrast enhancement are located mainly in the posterior columns, posterior horns, or lateral columns at the cervical or thoracic levels (41, 62). The white matter lesions can be indistinguishable from those of other demyelinating diseases (Fig. 3) (62).

Examination of the cerebrospinal fluid (CSF) may show mild lymphocytic pleocytosis, moderate increases in levels of protein, oligoclonal bands, and a high local synthesis of HTLV-1 antibodies (33, 47). The HTLV-1 provirus can be found in CSF cells of HAM/TSP patients. The increase in the proviral load in this fluid has been associated with the progression of myelopathy (47).

Neurogenic bladder is common in patients with HAM/TSP, and ultrasound (US) and video-urodynamic studies are the usual methods to define the diagnosis (63). Sonographic evaluation of the urinary system allows the study of the kidneys, the lower urinary tract, and the bladder. Many kidney disturbances can occur due to HAM/TSP neurogenic bladder. US evalua-
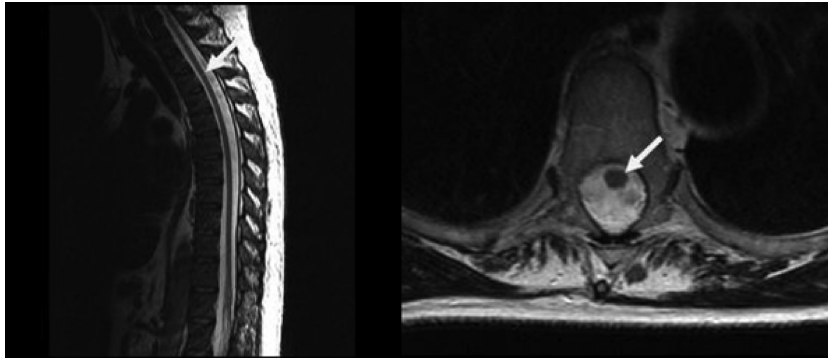
FIG. 2. MRIs showing thoracic cord atrophy (white arrow) in a patient with HAM/TSP.

tion determines the renal size and parenchyma detail, enlargement of the ureters, hydronephrosis, and kidney stones. Neurogenic bladder leads to incomplete emptying and chronic inflammation of the bladder. Stone formation and acquired diverticula are possible complications (87).

The study of urodynamics is useful for establishing the bladder pattern and for choosing the best therapeutic approach. This evaluation identifies the storage pressures, the residual volume, and voiding dysfunctions, which are important for the planning of treatment strategies. Cystoscopy is a method that complements bladder evaluation, since it allows a direct view of its contents and mucosa aspect (87).

Treatment and prognosis. The individual immune response and proviral load define the prognosis, since there is no curative treatment. Corticosteroids, IFN-α, and IFN-β1a have shown limited results (36, 67, 73). The combination of two nucleoside analogues (zidovudine and lamivudine) was evaluated in a randomized, double-blind, placebo-controlled study, and no clinical improvement was observed (95). However, in that work, the patients had advanced myelopathy, which could be considered a limitation of the treatment response.

An increase in the proviral load was observed for HAM/TSP patients undergoing corticosteroid treatment (93). Conversely, antiretroviral drugs caused a decrease in the load (95). These observations indicated that the proviral load in the blood may be of value to monitor disease activity in therapeutic trials (72). The proviral load in the CSF may be a more accurate biomarker of HAM/TSP progression than the load in the blood (31). More studies involving randomized controlled therapeutic trials may clarify the value of the proviral load to define disease control.
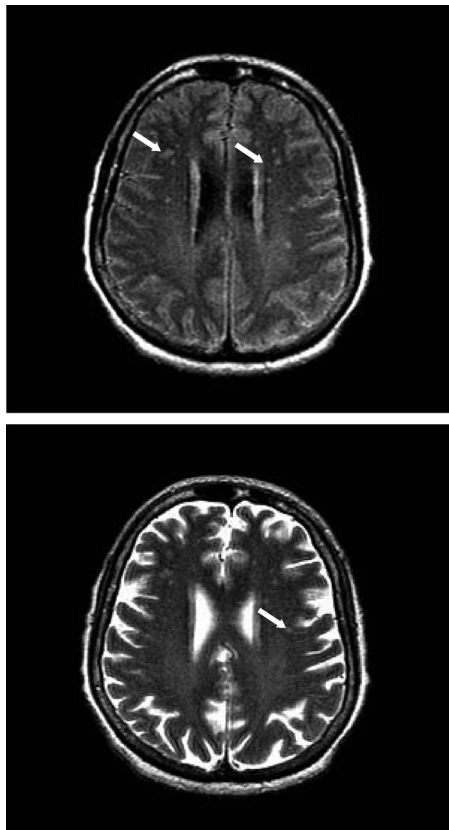

FIG. 3. Brain MRI performed with 1.5-T equipment (sagittal T2 weighted; axial FLAIR, T1- and T2-weighted images). (Top) T1-weighted images following venous paramagnetic contrast at three planes. (Bottom) T2-weighted MRI of the brain reveals punctate nodular discrete hyperintense foci without a mass effect in the periventricular and subcortical white matter. These lesions do not increase.

HTLV-1-Associated Uveitis

Ophthalmological disturbances related to HTLV-1 include vasculitis, exudation or degeneration of the peripheral retina, and keratoconjunctivitis sicca (61, 81), and HAU is an accepted entity associated with this viral infection (61, 69). Middle-aged HTLV-1-infected adults of both genders are the target population. HAU is characterized by a granulomatous or nongranulomatous reaction accompanied by vitreous opacities and retinal vasculitis with rare exudative retinochoroidal alterations in one or both eyes (61). It can occur as the only HTLV-1 manifestation or can be associated with HAM/TSP. Uveitis usually occurs as an isolated ophthalmological alteration (69). Qualitative lachrymal film defects have been shown to be frequent (81). Sicca syndrome associated with HTLV-1 differs from this ocular manifestation in primary or secondary Sjögren's syndrome, because it does not reveal any of the immunological alteration related to a rheumatologic disease.

Clinical characteristics and diagnosis. Characteristic symptoms have been described as "flying flies" and visual blurring of

acute or subacute installation (61, 69). In patients with HAM/TSP, uveitis was more frequent among those with an earlier onset of HAM/TSP and in patients with severe motor disability (58). HAU has clinical characteristics that can vary according to geographic area. In the Caribbean and Brazil, the corneal disease observed for HTLV-1-infected patients was not described for Japanese patients (58, 59, 61, 81).

Treatment and prognosis. The treatment of uveitis is based on topical and systemic corticosteroids. The response to therapy is satisfactory, as is the visual prognosis, although recurrence is common. Lubricating medication is the most important aid to treat mild and moderate keratoconjunctivitis sicca. Lubricating drops are used to reduce morbidity and to prevent ocular complications such as corneal ulcers.

Concerning prognosis, the immune system of patients with HAU has abnormalities similar to those seen for patients with HAM/TSP, such as elevated proviral load, the overproduction of proinflammatory cytokines, and the presence of HTLV-1 provirus in the spinal fluid (42, 75, 93). A significant elevation in levels of $CD4^+$ $HLA-DR^+$ and $CD8^+$ $HLA-DR^+$ cells and ocular abnormalities were demonstrated for patients with advanced HAM/TSP (81). Moreover, among asymptomatic HTLV-1 carriers, individuals with HAU presented immunological disturbances similar to those for HAM/TSP, and asymptomatic carriers without HAU presented a normal immunological profile (81). These results suggest the HAU can be either an independent inflammatory disease associated with HTLV-1 or, perhaps, a predictor of HAM/TSP.

Dermatological Conditions Associated with HTLV-1

Dermatological lesions are commonly associated with HTLV-1. Their importance is a special topic because cutaneous involvement in an apparently asymptomatic carrier has been considered a premonitory indication of the future development of either ATL or HAM/TSP.

Infective dermatitis (ID) and crusted scabies have been associated with HTLV-1 seropositivity in regions of endemicity and have also been reported for patients with ATL and HAM/TSP (8, 44). Cutaneous lesions in asymptomatic HTLV-1 carriers have also been found (29).

ID. ID was the first pediatric syndrome associated with HTLV-1 infection (44). It is characterized by a severe and relapsing eczematous disease with lesions involving the scalp, neck, external ear, axillae, and groin (44, 76). Fluid nasal discharge and crusts in the nostrils are common, as is blepharoconjunctivitis. Follicular papules and pustules on affected areas were noticed. Positive cultures for *Staphylococcus aureus* and beta-hemolytic *Streptococcus* were found for the nostrils or skin (44, 76). An adequate response to systemic antibiotics and topical steroids is usually obtained, although relapse is common (44). Long-term use of antibiotics has been recommended.

Differential diagnosis with other eczematous diseases is mandatory, since histological characteristics are not distinctive. Emphasis should be given to the differential diagnosis with atopic and seborrheic dermatitis. In atopic dermatitis, the distribution and morphological aspects of the lesions are similar to those seen for ID, in which the infection is more evident, with exudation and fetid odor (43). Conversely, in seborrheic dermatitis, the lesions are erythematous and scaly. It occurs

predominantly during childhood (76). Laboratory parameters such as the erythrocyte sedimentation rate, immunoglobulin level, CD4 and CD8 cell counts, and CD4/CD8 ratio, when elevated, must be considered when evaluating a patient with suspected ID, along with positivity for HTLV-1 (43).

ID cases occur mainly in tropical regions where HTLV-1 is endemic, such as Jamaica, and few cases in Japan have been described (76). This HTLV-1-associated dermatological lesion has been correlated with vertical transmission and long-term breastfeeding (44, 76). ID was found to be related to ATL and HAM/TSP (51, 71, 76). In an evaluation of severe and relapsing eczematous conditions observed for children in areas where HTLV-1 is endemic, a serological test for this virus should be considered (76).

CS. Crusted scabies (CS) is a severe variant of scabies, and the main characteristic is crusted lesions located over exposed areas, with millions of parasites. The link between CS and immunosuppression is well established (85). In Brazil, severe CS (more than 80% of the body area affected) was strongly associated with HTLV-1 infection and, to a lesser degree, with HIV infection (8). In Peru, the association was also shown (7). CS diagnosis can be done by scraping the lesion and obtaining a demonstration of numerous scabies mites. Treatment with oral ivermectin is recommended; relapses may occur. Special treatment protocols are recommended for severe cases (85).

Skin abnormalities related to ATL. ATL is generally categorized into four forms: acute, chronic, smoldering, and lymphoma types (89, 96). In a Brazilian ATL series of cases, 67% of the individuals had cutaneous lesions (6).

The acute form comprises 55 to 75% of all cases of ATL (89). In chronic ATL, skin lesions can be related to inflammatory reactions, immunosuppression, or direct infiltration of the skin by neoplastic cells. Lesions observed for chronic and smoldering variants of ATL can be similar to those seen for mycosis fungoides patients. (6, 96, 100). Monoclonal integration of provirus DNA is mandatory as diagnostic proof of chronic and smoldering ATL, since the histopathological characteristics of both are similar to those seen for mycosis fungoides (6). Many types of skin lesions have been related to HTLV-1, such as macular, papular, nodular, and tumoral lesions, with erythema, desquamation, and erythroderma. The skin involvement in an otherwise asymptomatic individual carrying HTLV-1 may be an indicator of smoldering ATL (6, 30).

Skin abnormalities in HAM/TSP. Acquired ichthyosis has been shown to be common in patients with HAM/TSP (60). The involvement of the autonomic nervous system was suggested to explain the pathophysiology, although direct damage of the skin by infected cells is another possibility (45). Keratinocyte activation, with the induction of alternative keratinization pathways probably depending on the cytokine liberation of infected cells situated in dermal infiltrates, was also proposed as a mechanism for acquired ichthyosis (60).

Other dermatological conditions described for HAM/TSP include candidiasis, palmar erythema, dermatophytosis, and folliculitis decalvans (45).

Skin abnormalities in asymptomatic HTLV-1 carriers. A cross-sectional study of Brazilian candidates for blood donation demonstrated a predominance of skin disease in asymptomatic patients infected with HTLV-1 in comparison to seronegative cases. Diseases associated with HTLV-1 in that study

were dermatophytic infections, seborrheic dermatitis, and acquired ichthyosis (29). In a Jamaican cohort study, the presence of atopic and seborrheic dermatitis was also associated with seropositivity for HTLV-1. Both conditions were already associated with hyperreflexia but without a definite HAM/TSP diagnosis (51).

OTHER HTLV-1-ASSOCIATED ABNORMALITIES

Opportunistic Infections

Opportunistic infections have been associated with acute ATL (96). HTLV-1-infected carriers seem to have an increased risk of acquiring strongyloidiasis, indicating a possible subclinical immune deficiency. HTLV-1-infected individuals from areas where *Strongyloides stercoralis* is highly endemic should probably undergo examination for stool ova and parasites, utilizing serial exams to increase sensitivity. Other infections associated with HTLV-1 in case reports include Norwegian scabies, disseminated molluscum contagiosum, and extrapulmonary histoplasmosis (8).

Rheumatic and Autoimmune Conditions

Inflammatory rheumatic conditions, including rheumatoid arthritis and Sjögren's syndrome, have been reported for HTLV-1-infected individuals, and increased proviral load has been associated with HTLV-1 infection (57, 82, 101).

Other autoimmune conditions associated with HTLV-1 include endemic polymyositis, bronchoalveolar pneumonitis, and autoimmune thyroiditis (35, 37, 40). In most of these reports, HTLV-1 proviral sequences can be readily detected, while viral antigen expression is low or absent in areas with extensive lymphocytic infiltration (68). It was suggested previously that restricted viral gene expression by antigen-presenting cells in the infected tissues triggers a vigorous $CD4^+$ and $CD8^+$ immune response against HTLV Tax or some other gene product (68). HTLV-1 was also associated with fibromyalgia in a case-control study with prevalent HTLV-1 cases (18).

Inclusion Body Myositis and Polymyositis

Muscle inflammation has been associated with HTLV-1 (56). It can be the single manifestation of the disease, or it can be associated with HAM/TSP. Patient complaints are myalgia and proximal muscle weakness. Laboratory tests show an elevated erythrocyte sedimentation rate and creatine kinase level. Muscle biopsy specimens show a myopathic pattern of inflammation.

Polyneuropathy

Peripheral neuropathies in HTLV-1-infected patients with and without HAM/TSP have been described (2). Polyneuropathy is usually asymmetric, sensory motor, axonal, or of a mixed type. The major complaints are hypoesthesia in a stock-and-glove distribution, paresthesias, and burning of the lower limbs. For this reason, HTLV infection should be investigated for individuals with polyneuropathies of unknown origin.

Electroneuromyography of these patients shows abnormalities in peripheral nerves that consist of minimal increases in the distal latencies with moderated slowing of the proximal waves and of the distal conduction velocities along the peroneal and sural nerves.

Psychiatric Disorders

Among asymptomatic HTLV-1 carriers, a high rate of depression was found compared to noninfected individuals. Depression could be related to the psychological impact of the incurable state or could be related to a biological effect of the retroviral infection (91).

PREVENTION

The prognosis for ATL and HAM/TSP is poor, and no vaccine is yet available. For HAM/TSP, a long-lasting, progressive disease, the financial cost for the individual, the family, and the health system is very high. In this sense, public health interventions such as counseling and education of high-risk individuals and populations are of paramount importance (10).

With the implementation of a program to prevent transfusion-transmitted HTLV-1 in Japan in 1986, many countries in areas where the disease is endemic started to implement systematic and permanent screening of all blood donors (79). Screening of blood donor candidates has been shown to be an effective strategy in preventing HTLV-1 transmission. For areas where the disease is not endemic, reports showed that the risk of HTLV-1 infection might be enhanced in some selected donor populations, recommending the implementation of policies for selective donor recruitment. However, more cost-effective strategies for blood donation screening need to be designed and evaluated for developing countries, given the high cost of imported test kits. Blood transfusion still represents a risk of HTLV-1 infection for recipients in most African countries as well as for other less developed areas that lack appropriate public policies and infrastructure of transfusion services (53, 84).

HTLV-1-seropositive individuals should be advised not to donate blood, semen, organs, or milk, where milk banks are available. Prevention of mother-to-child transmission would probably have the most significant impact on the occurrence of HTLV-1 infection and associated diseases.

Prenatal screening for HTLV-1 should be implemented in specific geographical areas, combined with counseling of seropositive mothers regarding transmission through breastfeeding. Avoidance of breastfeeding is fundamental, since it is the major form of vertical transmission of HTLV-1 (11). Due to the risk of malnutrition in developing countries, public health policies should consider this adverse effect in less developed countries and recommend an alternative feeding formula for children at risk of acquiring HTLV-1 infection through mother's milk (11, 52). The practice of cross-feeding should also be contraindicated due to the possibility of a "milk mother" being seropositive as well. In the case of pregnancy, a cesarean section should be recommended, to minimize the risk of perinatal transmission.

Recommendations to prevent sexually transmitted infections should be emphasized, including condom use and avoiding multiple and unknown sexual partners and paying or receiving money for sex. When one of the partners in a stable

relationship is negative, the need for condom use should be emphasized.

Counseling and education of intravenous drug users (IDU) to implement harm reduction practices may be effective in preventing HTLV-1 infection in this population group.

Psychological and social problems such as depression, increased anxiety, difficulty in establishing and maintaining relationships, and fear or guilt about pregnancy are common in HTLV-1-infected individuals and should be dealt with accordingly. Access to correct information about HTLV infection is very important. Confusion with HIV is common, even in health care settings, and leads to unnecessary stress on the patient, which is frequently associated with self-destructive thoughts (32).

Counseling should include orientation about the transmission of the virus and the possible source of the infection and an offering of testing to the partner/spouse and children. This is especially true when counseling blood donor candidates, because they are usually young, asymptomatic, and of a reproductive age. In our experience, when counseled about pregnancy and the avoidance of breastfeeding, female donors are usually compliant, and therefore, transmission may be blocked.

CONCLUSION

HTLV-1 should be added to the list of diseases that are preventable with safe sex, thus being a further stimulus to the use of condoms and to the adoption of safe sexual behavior. The development of an effective and safe vaccine as well as preventive measures in blood banks and prenatal care settings in areas of endemicity should be emphasized (21).

Although the incidence of ATL and HAM/TSP is found to be relatively low among individuals with HTLV-1 infection, ranging from 5 to 10% during a person's lifetime, the diseases are generally severe and progressively incapacitating.

Therefore, the prevention of virus transmission is advantageous not only at the individual level but also in the public health setting as well. Despite this, considerable effort is continuously being done by researchers to prove to health officers in countries where the disease is endemic that HTLV-1 infection should be prevented, and it is usually a neglected disease, with the majority of patients worldwide ignoring the source of their illness.

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