HUMAN T-CELL LYMPHOTROPIC VIRUS-I IN LATIN AMERICA

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EPIDEMIOLOGY

The first human retrovirus, human T-cell lymphotrophic virus type I (HTLV-I), was simultaneously discovered in the United States and Japan in 1980 and associated with adult T-cell leukemia/lymphoma (ATLL) patients. Promptly thereafter, seroepidemiologic studies revealed a high HTLV-I seropositive rate (>10%) among healthy adults in southwestern Japan (mainly in Okinawa and Kyushu Island) and moderate rates in the Caribbean, West Africa, and recently in Colombia, Brazil, Peru, Papua New Guinea and Australia.

HTLV-I Transmission

The transmission of HTLV-I involves several cells but mainly CD4 lymphocytes. Although transmission occurs in a manner similar to that described for HIV, there are important differences because of the requirement of infected lymphocytes as the basic underlying mechanism.
**Vertical Transmission**

Intrauterine transmission is very rare. Available information suggests that infection occurs through perinatal exposure and breast-feeding, especially when prolonged.7, 99, 100, 170, 172

In a retrospective study of 120 HTLV-I-infected Peruvian women and their offspring, infection was not detected in eight newborns that were not breast-fed but was documented in 5 of 36 (13.9%) of those who received maternal milk for less than 6 months, and in 23 of 76 (30.6%) of those breast-fed for more than 6 months (P<0.05) (E. Gotuzzo, unpublished data). In Colombia, one of the authors (C. Arango) and his coworkers have found similar rates of vertical transmission. Further evidence of the importance of breast-feeding is provided by studies in hyperendemic areas of Japan, where HTLV-I seropositive pregnant women abstained from breast-feeding, and as a result there was a marked decrease in the number of new infections among their children.128

**Parenteral Transmission**

HTLV-I is transmitted less effectively than HIV in whole blood transfusions, a situation whereby the latter virus infects more than 99% of the recipients. It is calculated that one unit of whole blood serologically positive for HTLV-I can infect 50% to 60% of recipients. The efficacy of transmission is decreased when blood is kept stored for more than 1 week. Transfusion of cryoprecipitate and fresh frozen plasma has not been associated with HTLV-I transmission.21, 140, 180, 213

Needle sharing by intravenous drug users (IVDUs) has been shown to be the most common route of HIV transmission in the United States, Italy, Spain, Brazil, and Argentina.181 HTLV-I can also be transmitted by this route, but the efficacy of transmission is very low. In fact, HTLV-II is currently more prevalent among IVDUs of these countries than HTLV-I.31, 91, 122, 141, 152, 200

HTLV-I seropositivity in blood banks of France, the United Kingdom, and the United States has been low, in the range of 0.005% to 0.0046%. In Latin America, studies have shown varied rates of seropositivity. For example, in Buenos Aires, Argentina, 4 of 12,846 donors were confirmed positive (0.032%); however, eight additional donors were positive by enzyme-linked immunosorbent assay (ELISA) but indeterminate by Western blot (WB). With the recent diagnostic technology advances, these donors would probably have been defined as positive, increasing the seropositivity rate to 0.2%. In Sao Paulo, from a total of 17,063 donors, 0.15% were HTLV-I positive; in Bello Horizonte, of 51,135 blood donors, 689 (1.35%) were repeatedly reactive.186 The overall seropositivity in all of Brazil in 1995 was around 1%.72 In Trinidad and Tobago, the overall infection rate in blood donors was 1.6%, but in multiply transfused patients, the rate was as high as 3.7%.48 In Paraguay, the detected infection rate was 1.1% (7 of 621) in blood donors.92
Epidemiologic studies conducted among the general population in Caribbean countries have shown that the prevalence of HTLV-I seropositivity (1) significantly increases with age; (2) is higher in females, specifically in low socioeconomic strata; and (3) correlates with a history of blood transfusion. Other studies performed in Brazil, Chile, Colombia, and Peru on the epidemiology of patients with tropical spastic paraparesis (TSP) have shown that a history of blood transfusion was an important risk factor for infection, ranging from 15% to 40%. In 1997, Fuentes conducted a survey of the National Program of Blood Banks in Peru (PRONAHEBAS). The results indicated that of 142,583 donors tested at 164 different blood banks, 2068 were HTLV-I positive (1.45%) at initial screening, and 1861 (1.2%) were confirmed positive on retesting.

A national survey of HTLV-I seropositivity associated with myelopathy (HAM) in Japan revealed that 20% (26/129) of positive cases had a history of blood transfusion compared with only 3% (41/129) in a healthy control group (OR = 7.7, P < 0.001). In the subsequent 2 years, screening blood for HTLV-I and discarding of blood from positive donors resulted in a 16% decrease in the number of reported cases of TSP/HAM.

In spite of the above information, recent publications about prevention of bloodborne diseases (such as the article by Schmunis and other communications published in the Pan American Health Organization (PAHO) bulletin that underscore the impact of blood quality in the prevention of HIV, hepatitis, Chagas disease, and other bloodborne infections transmitted through blood transfusion in Latin America) fail to comment about HTLV-I screening as carried out in Europe and the United States. In these countries, the ELISA test is performed in all donors because the procedure is cost-effective. In Latin America and the Caribbean, it is reasonable to conclude that it is especially important to screen for HTLV-I because of the available information and because of the high prevalence of infection among African Americans (3% to 10%), Japanese descendants (4% to 15%), and other ethnic groups (2% to 5%) as well as in blood donors (0.5% to 2.0%) coming from countries with high prevalence and living in the region.

**HTLV-I as a Sexually Transmitted Disease (STD)**

HTLV-I has been detected in the semen and cervical secretions of infected persons. Sexual intercourse is recognized as an important factor for HTLV-I transmission. Population studies in Japan suggest that male-to-female sexual transmission is more efficient than female-to-male. In one of these studies, after 10 years, 60% of women were infected when a man was the index case; however, only 0.1% to 1.0% of the men were infected when the index case was a woman. In Miyasaki, Japan, the risk factor for transmission within serologically discordant couples included older infected husbands, high antibody titers, and the presence of antitax antibodies. In one family study in Peru, 45% to 55% of stable sexual partners of index cases positive for HTLV-I were infected, but in
women the rate was 60% to 75% when the initial positive index case was the husband \((P<0.001)\) (E. Gotuzzo, unpublished data), supporting the concept of high efficacy of male-to-female transmission. In Latin America, there are important gender differences in sexual practices and seroprevalence of STDs that could partially explain these findings.\(^{210}\)

HTLV-I infection has been frequently recognized in female sex workers (FSW) in the United States.\(^{123}\) In Peruvian cities, prevalences are as high as 25% in Callao, 13.4% in Cuzco, 4.2% in Iquitos, and 7% in Lima. In all these studies, a critical risk factor was the time working as an FSW (in cases with more than 6 years, 16% were seropositive).\(^{81,238,256}\) In these studies, a positive syphilis serology was a frequently associated risk factor for HTLV-I infection. Other risk factors were a history of any STD \((P<0.001)\) in Cusco and infection with *Chlamydia trachomatis* in Lima \((OR=4.5; 95\% \text{ CI}, 1.5–13.4)\). Other studies have also suggested the association of HLTV-I with syphilis, herpes simplex virus type 2 (HSV-2), and genital ulcers in the Dominican Republic and Colombia. Transmission of HTLV-I was also described in homosexual men in Trinidad, Brazil, and Peru.\(^{34,45}\) In studies conducted in Peru in HIV patients, the number of sexual partners was an important associated risk factor.\(^{84,189}\)

The use of condoms is accepted as a factor reducing HIV infection in FSWs.\(^{138,177,211}\) The same finding was reported for HTLV-I transmission in two Peruvian studies involving the same risk factor population.\(^{81,231}\) In Lima, when condoms were used by more than 50% of the partners of FSWs for more than 3 years, their seropositivity odds ratio was 0.34 \((95\% \text{ CI}, 0.13–0.89)\), in comparison with FSWs that did not use condoms.\(^{81}\) In another study of clandestine FSW in Lima, when condoms were used by all of the partners, the infection rate of HTLV-I was only 1.7%, but when they did not use condoms or used them only occasionally, the infection rate rose to 10.3% \((OR=0.15; 95\% \text{ CI}, 0.03–0.86)\).\(^{231}\)

There is no doubt that HTLV-I is an STD in Latin America. The virus is found in semen and cervical secretions and is more effectively transmitted from males to females than from females to males. Seropositivity is more frequently observed in groups of high sexual risk such as FSWs and promiscuous men who have sex with men (MSM). It is associated with the number of sexual partners, time in prostitution activities, other STDs, and markers of promiscuity, and most importantly, sexual transmission can be significantly reduced by the consistent use of condoms.

## DISTRIBUTION OF HTLV-I AND II IN LATIN AMERICAN ETHNIC GROUPS

### Evolution of Language and Its Relationship with HTLV-I and II

Genetic evolution is the result of three main forces: mutation, selective pressure, and random genetic drift. The last mentioned refers to
fluctuations of the frequencies of an allele between successive generations. Smaller populations will have relatively high fluctuation of gene frequencies between generations compared with large populations, which can cause an allele to become fixed (frequency = 199%) or extinct (frequency = 0%) in a shorter period of time. Fission refers to excision of a proportion of the population without further contact with the parental individuals. Phylogenetic analysis is usually carried out in genes. Languages and genes are subjected to some common evolutionary forces. With some limitations, the concepts and techniques of phylogenetic analysis can also be applied to languages. A linguistic family is composed of a group of languages with enough similarities to suggest a common phylogenetic origin. There is a remarkable correspondence between genetic clusters and linguistic families. From a linguistic point of view, the pre-Hispanic inhabitants of America can be classified into three families: Amerindians (oldest), Na-Dene, and Eskimo-Aleutian (most recent). The Amerindian family can be subdivided into six subfamilies or primary branches: Northern, Central, Chibchan-Paezian, Andean, Equatorial-Tucanoan, and Ge-pano-Carib.

HTLV-I: Phylogenetic Studies and Relationship with Humans

After HTLV-I and II diverged, an Indonesian simian T-lymphotropic type I strain (STLV-I) and an Australo-Melanesian HTLV-I topotype sequentially appeared. Based on 7 estimated mutation rate of 0.4 to 2.5 x 10 substitutions per site, per year, this event occurred 140,000 to 850,000 years ago. This would have occurred before or soon after Homo sapiens was present on earth. Later, a group called cosmopolitan topotype evolved. This included Zairean and Afro-Indoamerican geographic phenotypes.

Epidemiology in Pre-Hispanic Inhabitants

HTLV-I has been found in members of at least two of the three families who populated pre-Hispanic America. Some reports indicate that a small proportion of Inuit, who are Eskimos from Alaska and Greenland, are HTLV-I seropositive. HTLV-I has been described in individuals from Nuu-Chaa-Nulth groups, who are northern Amerindians from British Columbia. HTLV-I has also been found in members of the Paez, Embera, Chachi, and Inga tribes from Colombia. The first three belong to the Chibchan-Paezian subfamily. HTLV-I has been reported in Mapuches and Huiliches in Chile and other members of the Andean subfamily. It has also been described in Quechus from Cuzco and Ayacucho. Its presence has also been noted among Sapaná from Paraguay and Tobas from Argentina. These two tribes belong to the Ge-Pano-Carib subfamily. We have found HTLV-I seroprev-
eralence of 1% and 0.8% among Emberá and Paez tribes. Seroprevalence increased with age in both groups, starting at the second decade. Seroprevalence was higher among females than males. This is consistent with cumulative lifetime infection and supports observations that sexual transmission is more efficient from male to female. HTLV-I and II infection has been demonstrated among several pre-Hispanic tribes, including the following: Navajo Indians, who belong to the Na-Dene family; the Northern branch of the Amerindians, represented by individuals from the Pueblo (Suny) and Seminole (Muskogee) tribes; tribes of the Chibchan-Pezian subfamily, including Guaymi from Panama and Tunebo, and Emberá from Colombia; the Andean subfamily, including members of the Inga tribe from Colombia and Mapuche, Huliches, and Alcalufe from Chile; the Guahibo and Wayu tribes from Colombia as well as Piaroa, Arara do Laranjal, and Muduruku from Brazil of the Equatorial-Tucanoan branch; Ge-Pano-Carib subfamily Indians, represented by Cayapo and Kraho from Brazil and Toba, Mataco, and Pilaga from Argentina; Tume Indians from Venezuela and Yaganes from Chile; and we have found a HTLV-I and II prevalence of 0.8% among the Emberá tribe in Colombia. There was no significant difference in prevalence by gender. A lifetime increase by age after the third decade was significant. Female preponderance has been reported in one study of Cayapo Indians in Brazil. An age-related increase in seroprevalence rate has also been described among Cayapo and Guaymi Indians. HTLV-I and II coinfection has been reported in different individuals of the following groups: Central African Pygmies from Zaire and Cameroon in Africa, Nuu-Chah-Nult in British Columbia in North America, Emberá and Inga in Colombia, and Tobas in Argentina.

Relationship Between Linguistic Evolution and the Presence of HTLV-I and II

Except for one tribe (Navajo), HTLV-II has been described only and in almost all subfamilies of Amerindian speakers. The genetic variability in America, particularly in South America, is the greatest in the world. This would be consistent with the hypothesis of frequent and sequential population fissions and isolation of small groups. This phenomenon probably occurred in the plains of the South American subcontinent and not in the Andes. Under these circumstances, a strong influence of drift leads to high genetic variability. Isolation and endogamy, practiced by some Amerindian tribes, may also have favored persistence of HTLV-II among them, if the virus was present in their ancestors. The Navajo tribe comes from South Na-Dene speakers. They and the Almosan (Northern Amerindian subfamily), represented, among others, by the Pueblo tribe, are derived from a common linguistic branch. Navajo ancestors probably represent fission from the Northern Na-Dene speakers that occurred more than 1 millennium ago. They likely admixed with neighboring Northern Amerindians, including Almosan.
could explain the presence of this virus among individuals of the only non-Amerindian tribe, if present originally only in Paleo-Indians, the Amerindian ancestors.

The linguistic branch that gave origin to Almosan and South Na-Dene is also phylogenetically related from a linguistic point of view to the one that originated Ge speakers. This could explain the presence of HTLV-II type A among Pueblo, Navajo, and Ge speakers. The latter are represented by Cayapo and Kraho tribes in Brazil.

In summary, HTLV-II has been reported from Pygmies in Africa, Mongolians, and Amerindians. Their common origin, according to a phylogenetic tree, goes back to the initial stock of Homo sapiens. It appears that this virus became incorporated into humankind before it diverged into different racial groups. A finding of microgeographic and macrogeographic clustering, as indicated by the absence of the virus in villages and regions adjacent to others with significant seroprevalent rates would establish a parallel between the forces that lead to fixation or extinction of certain genetic elements and these retroviruses. HTLV-I and II would share similar cofactors for transmission. The weight of each one could be different in each one of them.

It is possible that the conditions that lead to perpetuation of HTLV-I and HTLV-II differ in some ways. In the Andes, population density rose to levels higher than the rest of the subcontinent, where fission of small groups at short time intervals probably occurred. HTLV-I is prevalent in the Andes but not HTLV-II. These less stringent conditions would favor persistence of the more worldwide-distributed HTLV-I but not HTLV-II. The higher prevalence of HTLV-I among females may represent not only a predominant unidirectional route of transmission but also a larger reservoir for mother-to-child transmission. We found HTLV-I-positive individuals in both Paecs who live in the Andean highlands and Emberá who live in the lowlands. A report published in Argentina about HTLV-I showed various strains different from the African strains; the strains are more related to other South American countries and Canada with similar anthropological background.

A geographic independence in the distribution of HTLV-I and HTLV-II has been described. Population migration habits rather than altitude may explain these differences.

**Afro–Latin American Population**

In South America, where there is a strong presence of African Americans in some places, such as Tumaco (Pacific Coast, Colombia), Bahia (Brazil), and Chincha (Peru), the prevalence of HTLV-I ranges from 2% to 5% among healthy adult populations. (C. Sánchez Palacios, personal communication, 1998).

Two hypotheses have been advanced to explain the dissemination of HTLV-I subtype a (HTLV-Ia) in the New World. The first is related to an ancient introduction by Mongoloid migration over the Bering Strait.
or a post-Colombian introduction initially from Africa, through the slave trade. Blank in Colombia and Veronesi in Brazil estimated that HTLV-I could be post-Colombian. Recently, Van Dooren reported on the phylogenetic analysis of the LTR and env sequence of 13 HTLV isolates from four different ethnic Peruvian groups. The results supported the idea of multiple post-Colombian introduction of the African HTLV-Ia strain into the black Latin American population; probably, it spread to Andean groups when living together as occurred in Cuzco during the early seventeenth century.

Japanese Descendants

A serologic survey among Japanese migrants in Bolivia showed that 17% of the older migrants were positive for HTLV-I, especially for adults who came from Okinawa; and 4% to 7% of the next generation were positive. In Peru, a survey of 407 healthy volunteers with Japanese ancestors showed that HTLV-I infection rates were 15.8% for those born in Japan, 4% for the first generation born in Peru, and 0% for the second generation (P = 0.00001). Infection rates were higher among males than females (6.8% versus 3.2%), and the frequency was related to the origin of their ancestors (more frequent in Okinawa descendants). Similar observations were reported by Blattner in Hawaii, where the HTLV-I infection rates declined substantially among new generations of Japanese. In the Van Dooren phylogenetic study, the Japanese infection was related to different strains and was not the cause of dissemination of HTLV-I in Latin America as proposed by other investigators.

HTLV-I–ASSOCIATED DISEASES

As documented for all retroviruses, the cell infection is permanent and all patients are carriers and potential sources of infection. Several disease syndromes are associated with HTLV-I, and each syndrome may occur in 1% to 5% of the infected cases. The most common are TSP and ATLL; however, these have been recognized in association with other medical problems such as Strongyloides stercoralis infection, Norway scabies, and uveitis.

Tropical Spastic Paraparesis

For many years, neurologists from tropical regions had described cases of a chronic progressive paraparesis of unknown cause. In 1969, Mani et al, recognizing the clinical and histopathologic similarities among these patients, coined the general term tropical spastic paraparesis to denominate these syndromes. The precise cause of these myelopathies remained obscure until 1985, when Gessain and coworkers found that
most TSP patients from Martinique had antibodies to HTLV-I in their sera. These initial findings were soon confirmed by Rodgers-Johnson, who detected HTLV-I antibodies in serum and cerebrospinal fluid (CSF) of TSP patients from Jamaica and Colombia. Months later, Osame et al described the same association in patients from Kagoshima in southern Japan. Because these Japanese patients came from a nontropical region, the term TSP seemed inappropriate, and the authors proposed the new designation, HTLV-I–associated myelopathy. Soon it became clear that the diseases were the same, and in 1989, a consensus conference sponsored by the World Health Organization suggested the hybrid designation HTLV-I–associated myelopathy/tropical spastic paraparesis (HAM/TSP).

HAM/TSP is a disease predominantly found in southern Japan, the Caribbean, and South America. The prevalence of HAM/TSP coincides with the prevalence of HTLV-I in the general population; however, in Papua New Guinea, in spite of an extremely high prevalence of HTLV-I infection among certain groups, there are no reported cases of either ATLL or HAM/TSP. This may be because of a high level of divergence of the prevalent Melanesian strain of the virus.

The first description in Latin America of what was later called HAM/TSP was that of Zaninovic et al, who described spastic paraparesis of unknown cause among patients in Tumaco, Colombia. Four years later, these patients were found to be infected with HTLV-I. Since then, many reports of cases of HAM/TSP from Latin American countries have appeared in the literature. Most of these cases come from Brazil, Colombia, Chile, and Peru. Patients have also been described in Panama, Ecuador, Argentina, the Dominican Republic, Paraguay, Cuba, and Caribbean countries.

HAM/TSP is a myelopathy characterized anatomically by a chronic, progressive, low-grade inflammatory process heralded by parenchymal infiltration of memory CD4 cells. The inflammation involves both the gray and white matter of the spinal cord and progresses for more than 3 years after the onset of neurologic symptoms, resulting in preferential degeneration of the white matter. In patients with an evolution of more than 9 years, however, the spinal cord lesions appear degenerative rather than inflammatory. Both the inflammation and the white matter degeneration are most conspicuous in the lower thoracic cord. The lateral funiculus is always and most severely affected. Although the parenchymal tissue degeneration is not confined to any particular long tract, symmetric degeneration of the lateral pyramidal tract is evident in all cases. The involvement of the posterior and anterior funiculi is variable, and neurons are relatively well preserved.

The pathogenesis of HAM/TSP is still a matter of debate in the literature. Whereas only a small proportion of HTLV-I–infected individuals develop HAM/TSP (1% to 4%), the mechanisms responsible for the progression of an HTLV-I carrier state to clinical disease are not clear. No specific sequence differences have been found between HTLV-I recovered from HAM patients, patients with ATLL, and HTLV-I–infected carriers. According to Osame’s hypothesis, the supply of infected CD4
cells via the blood to the CNS is essential for the development of CNS lesions. Both anatomically determined hemodynamic conditions and adhesion molecule–mediated interactions might contribute to the localization of the lesions. Following an induction of the HTLV-I antigens on the surface of infected T cells in the CNS compartment, expansion of the responses of immunocompetent T cells against the viral protein may result in CNS tissue damage, which may be mediated by released cytokines such as tumor necrosis factor α (TNF-α). CTL-induced apoptosis of T lymphocytes may be one of the possible mechanisms of eliminating HTLV-I–infected cells from the CNS lesions in HAM/TSP. Protection from apoptosis by expression of bcl-2 oncoprotein may explain the long-standing inflammatory process in the CNS of HAM/TSP.\textsuperscript{182}

Izumo et al performed a detailed neuropathologic analysis of seven Japanese autopsy patients with HAM/TSP. Inflammatory infiltrates of mononuclear cells and degeneration of myelin and axons were noted in the middle to lower thoracic spinal cords and were continuously extended to the entire spinal cord. Horizontal distribution of inflammatory lesions was symmetric at any spinal level. Immunohistochemical analysis demonstrated T-cell dominance. The numbers of CD4 cells and CD8 cells were equally present in patients with a shorter clinical course. Apoptosis of helper/inducer T cells was observed in the presence of TIA1\textsuperscript{+} cytotoxic T cells in these active inflammatory lesions. Inflammatory infiltrates were markedly decreased, and CD8\textsuperscript{+}/TIA1\textsuperscript{−} T cells were predominant over CD4 cells in patients with a prolonged clinical course. HTLV-I proviral DNA amounts in the freshly frozen spinal cord measured by quantitative polymerase chain reaction (PCR) were well correlated with the numbers of infiltrated CD4 cells. In situ PCR of HTLV-I proviral DNA demonstrated the presence of HTLV-I–infected cells exclusively in the mononuclear infiltrates of perivascular areas. These findings suggest that the target of the inflammatory process seen in HAM/TSP lesions may be HTLV-I–infected CD4 cells infiltrating the spinal cord.\textsuperscript{112}

The diagnosis of HAM/TSP is based on clinical and laboratory data. In summary, the patient should present unequivocal signs and symptoms of a myelopathy along with clear evidences of HTLV-I infection.\textsuperscript{11}

To try to overcome diagnostic difficulties for epidemiologic studies, Osame et al\textsuperscript{184} suggested the following classification:

- **Definite HAM**
  Slowly progressive paraparesis caused by a symmetrical myelopathy that affects mainly the pyramidal tracts. Antibodies to HTLV-I in serum and CSF.

- **Probable HAM**
  Slowly progressive paraparesis due to a symmetric myelopathy that affects mainly the pyramidal tracts in a patient with antibodies to HTLV either in serum or in CSF (not in both). Atypical myelopathy in a patient with antibodies to HTLV in both serum and CSF.
The widely accepted diagnostic guidelines for HAM/TSP are summarized in Table 1. According to these guidelines, "the florid clinical picture of chronic spastic paraparesis is not always seen on the patient's first visit. A single symptom or physical sign may be the only evidence of early HAM/TSP."241

Besides typical HAM/TSP, other neurologic manifestations, such as polymyositis,21,156 motor neuron disease,2,97,136,221 peripheral neuropathies,1,23,173,208 encephalomyelitis,125,226 spinocerebellar degeneration,126

**Table 1. GUIDELINES FOR THE DIAGNOSIS OF HAM/TSP**

<table>
<thead>
<tr>
<th>Age and Sex</th>
<th>Onset</th>
<th>Main neurologic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostly sporadic,</td>
<td>Usually</td>
<td>Chronic spastic paraparesis, which usually progresses slowly, but</td>
</tr>
<tr>
<td>and adult females</td>
<td>insidious</td>
<td>may remain static after initial progression</td>
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</tbody>
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<table>
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<tr>
<th>Less frequent neurologic findings</th>
<th>Other neurologic manifestations associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness of the lower limbs, more marked</td>
<td>Muscular atrophy, fasciculations, polymyositis</td>
</tr>
<tr>
<td>Bladder disturbance usually an early feature;</td>
<td>Pulmonary alveolitis, uveitis, Sjogren's syndrome,</td>
</tr>
<tr>
<td>Sensory symptoms are more prominent</td>
<td>Presence of HTLV-I antibody or antigen*</td>
</tr>
<tr>
<td>Low lumbar pain with radiation to the legs is</td>
<td>Presence of HTLV-I antibody or antigen*</td>
</tr>
<tr>
<td>Vibration sense is frequently impaired</td>
<td>Presence of HTLV-I antibody or antigen*</td>
</tr>
<tr>
<td>Hyperreflexia of lower limbs, often with clonus and Babinski's sign</td>
<td>Presence of HTLV-I antibody or antigen*</td>
</tr>
<tr>
<td>Hyperreflexia of upper limbs frequently with positive Hoffmann's and Tromms' signs</td>
<td>Presence of HTLV-I antibody or antigen*</td>
</tr>
<tr>
<td>Exaggerated jaw jerk in some patients</td>
<td>Presence of HTLV-I antibody or antigen*</td>
</tr>
<tr>
<td>Cerebellar signs, optic atrophy, deafness, nystagmus, other cranial nerve deficits, hand tremor, absent or depressed ankle jerk</td>
<td>Presence of HTLV-I antibody or antigen*</td>
</tr>
<tr>
<td>Peripheral neuropathy, polyradiculopathy, cranial neuropathy, meningitis, encephalopathy</td>
<td>Presence of HTLV-I antibody or antigen*</td>
</tr>
<tr>
<td>Arthropathy, vasculitis, ichthyosis, cryoglobulinemia, monoclonal gammopathy, adult T-cell leukemia/lymphoma</td>
<td>Presence of HTLV-I antibody or antigen*</td>
</tr>
</tbody>
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<tr>
<th>Laboratory findings</th>
</tr>
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<tbody>
<tr>
<td>Blood</td>
</tr>
<tr>
<td>Presence of HTLV-I antibody or antigen*</td>
</tr>
<tr>
<td>Lobulated lymphocyte may be present</td>
</tr>
<tr>
<td>Viral isolation when possible</td>
</tr>
<tr>
<td>Presence of HTLV-I antibody or antigen*</td>
</tr>
<tr>
<td>Lobulated lymphocyte may be present</td>
</tr>
<tr>
<td>Mild to moderate increase of protein may be present</td>
</tr>
<tr>
<td>Viral isolation when possible</td>
</tr>
</tbody>
</table>

*Present in blood and CSF

Modified from WHO Guidelines in HTLV-I Diagnosis.
Pandysautonomia or autonomic failure,\(^6,^{248}\) and hypertrophic pachymeningitis,\(^{121}\) have been described in association with HTLV-I. These associations suggest that the neurologic spectrum of HTLV-I-induced disease is larger than previously thought.

The risk for development of HAM/TSP among HTLV-I carriers is also a matter of debate in the literature. It has been estimated to vary from 0.25% among Japanese patients\(^{118}\) to 2.4% among HTLV-I–infected blood donors from the United States.\(^{163}\) This risk can be higher, as suggested by an ongoing study of blood donors from Brazil, where 5% had HAM/TSP (Ana C. Leite, MD, personal communication, 1999).

Kramer et al sought to quantify the risk of HAM/TSP associated with HTLV-I infection and cofactors associated with this disease among infected individuals in Jamaica. One cofactor associated with the risk of HAM/TSP was young age at initial heterosexual intercourse. Among individuals who reported early age at initial sexual intercourse, an increased risk of HAM/TSP was also associated with having recorded more than five lifetime sexual partners. Neither an early age at initial sexual intercourse nor the number of lifetime sexual partners was a risk factor for ATLL. These data seem to support the notion that HAM/TSP is associated with sexually acquired HTLV-I infection, whereas ATLL is not.\(^{133}\)

Patients with HAM/TSP have higher antibody titers and virus load compared with asymptomatic HTLV-I carriers.\(^{76, 127}\) This information has led to the hypothesis that HLA alleles control HTLV-I provirus load and influence susceptibility to HAM/TSP. In fact, it has been recently shown that after infection with HTLV-I, the class I allele HLA-A*02 halves the odds of HAM/TSP, preventing 28% of potential cases of HAM/TSP. HLA-A*02(+) healthy HTLV-I carriers have a proviral load that is one third that of HLA-A*02(−) HTLV-I carriers. An association of HLA-DRB1*0101 with disease susceptibility was also identified, which doubled the odds of HAM/TSP in the absence of the protective effect of HLA-A*02.\(^{113}\)

HTLV-I leads to systemic manifestations in which the neurologic involvement is only one part. HAM/TSP can be associated with other HTLV-I–related manifestations such as pulmonary alveolitis,\(^{223}\) uveitis,\(^{171}\) arthritis,\(^{128}\) dermatitis,\(^{12, 139}\) Sjögren syndrome,\(^{148, 168}\) Behçet’s disease,\(^{116}\) thyroid disease,\(^{119, 153}\) crusted scabies,\(^{22}\) cystitis, and prostatitis.\(^{179}\) In some instances many of these systemic diseases can be observed at the same time.\(^{69}\) The occurrence of ATLL and HAM/TSP in the same patient is rare.\(^{68, 105, 117, 161, 195, 228, 234, 247}\)

A variety of systemic laboratory abnormalities can be found in patients with HAM/TSP. These typically include the presence of flower cells in blood smears, hypergammaglobulinemia, increased proportion of CD4 cells, positive VDRL and Lyme serologies, and the presence of autoantibodies such as the rheumatoid factor.\(^{206}\)

The most common findings in the CSF of HAM/TSP patients are a moderate pleocytosis and elevated protein content.\(^{158, 222}\) In addition,
oligoclonal IgG bands, increased levels of some cytokines, such as neopterin, TNF-α, interleukin (IL)-6, and interferon (IFN) γ, and increased intrathecal antibody synthesis specific for both HTLV-I core and envelope antigens have also been described. Apparently, the CSF profile changes with time. Although CSF inflammatory alterations can persist over a 10-year period, they tend to become slight or even absent after the second year of the evolution of the disease.

Magnetic resonance (MR) imaging is the study of choice for noninvasive spinal cord and brain evaluation of HAM/TSP patients. Cerebral white matter lesions and spinal cord atrophy have been consistently observed in patients with HAM/TSP, but the exact frequency and clinical relevance of these findings remain to be elucidated. In a recent published series, cerebral white matter lesions occurred in 52% of the patients, and spinal cord atrophy in 74%. There was no significant correlation between these abnormalities and the clinical features studied. These findings suggest that MR imaging is useful for detection of cerebral and spinal cord abnormalities in these patients. The absence of correlation between cerebral white matter lesions and either patient age or risk factors for cardiovascular disease strengthens a possible association between the leukoencephalopathy and neural infection.

Castillo et al examined 22 HAM/TSP patients from Chile and found abnormalities in the somatosensory evoked potentials (SSEPs) in 19 (86.3%), reflecting the involvement of the posterior columns of the spinal cord. Visual evoked potentials (VEPs) and brain stem auditory evoked potentials (BAEPs) were normal in 18 patients. Peripheral nerve conduction was normal in all but one, who showed discrete slowness of the motor conduction velocity in the peroneal nerves. Electromyography was normal in 15 cases in which it was performed. More recently, Moritoyo et al examined lower limb somatosensory evoked potentials (LSEPs) in 96 Japanese HAM/TSP patients. Central sensory conduction time (CSCT) was abnormal in 42 cases. A highly significant correlation was found between CSCT and disability score. Such a correlation was not found between CSCT and other clinical findings, onset of illness, illness duration, and serum and CSF antibody titers to HTLV-I and vibratory sensation. There was no difference in the mean CSCT between the cases with sensory impairment and those without it. Cases with delayed CSCT and normal sensation suggest that LSEPs can be capable of detecting subclinical lesions of the spinal cord in HTLV-I-infected individuals. LSEPs can also be useful in estimating the disability of HAM/TSP patients.

Urodynamic studies and urologic evaluation reveals that both irritative and obstructive symptoms coexisted in HAM/TSP patients. A clear cause of urinary frequency is detrusor hyperreflexia at the filling phase, which is found in more than half of the patients; however, decreased effective bladder capacity resulting from a large amount of residual urine is another possible cause. Detrusor sphincter dyssynergia is the main cause of difficulty of urination, but in some cases, underactive
detrusor activity at voiding is also a factor. Hydronephrosis is observed infrequently. Urinary infection is common, reported in about 35% of patients at first visit.\textsuperscript{107}

\textbf{Differential Diagnosis}

The diagnosis of HAM/TSP is based on a compatible clinical presentation of progressive myelopathy, plus the following: a CSF with signs of low-grade inflammation and a characteristic immunoglobulin profile MR image showing spinal cord atrophy or diffuse T2-bright abnormalities, presence of Western blot–confirmed HTLV-I-specific antibodies in the serum and CSF, and exclusion of other causes of progressive myelopathy including compression, B\textsubscript{12} deficiency, HIV infection, multiple sclerosis, Lyme disease, and genetic myelopathies. Living in an endemic area, transfusion exposure, intravenous drug use, sexual promiscuity, and having other HTLV-I systemic manifestations strengthen the diagnosis.

\textbf{Treatment Alternatives}

Several treatment approaches have been tried for HAM/TSP, but most did not include a proper placebo-controlled, double-blind design. Recently, Nakagawa et al reported the results of therapeutic trials of 200 patients with HAM/TSP from Kagoshima, Japan. Motor disability was improved by more than one grade in 69.5\% (91/131) of patients receiving oral prednisolone, 50\% (3/6) of those receiving eperisone hydrochloride only, 43.8\% (7/16) of those subjected to blood purification—lymphocytapheresis and plasmapheresis—methods, 40.0\% (2/5) of those receiving intrathecal injection of hydrocortisone, 30.0\% (3/10) of those receiving intravenous injection of high-dose methylprednisolone, 23.3\% (10/43) of those receiving α-interferon (αIFN) (intramuscular injection and inhalation), 22.2\% (2/9) of those receiving azathioprine, 20.0\% (4/20) of those receiving high-dose vitamin C, 16.0\% (4/25) of those receiving erythromycin, 12.5\% (3/24) of those receiving salazosulfapyridine, 11.8\% (2/17) of those receiving mizoribine, 7.1\% (1/14) of those receiving fosfomycin, and 6.3\% (1/16) of those receiving thyrotropin-releasing hormone. Although the results were a synopsis of different treatments given as an open trial, they considered that immunomodulatory therapies had some beneficial effects for HAM/TSP and that the pharmacologic effects of these agents were related to the improvement of the disease.\textsuperscript{107}

To date, the only double-blind, placebo-controlled treatment study in HAM/TSP is the one by Izumo and colleagues, who used αIFN.\textsuperscript{111} They concluded that HAM patients may be safely treated with αIFN at daily parenteral doses of 3 million units for 4 weeks. In another study of αIFN in HAM/TSP, the absolute number of peripheral blood lymphocytes harboring the HTLV-I genome decreased significantly during the therapy period (28.6 + / − 16.6% reduction). The autopro\textsuperscript{l}loration of
CD4+ T clone cells from a single cell culture was markedly depressed even after the cessation of αIFN in the responders who completed long-term therapy. In addition, the CD8+DR+ T cells in the peripheral blood and soluble IL-2 receptor levels in the sera increased significantly during the treatment. These results suggest that the reduction of HTLV-I proviral DNA load and immunomodulation by long-term IFN-α therapy contributed to the clinical benefits.242

**Disease Progression**

HAM/TSP is considered a disease with a slow onset and chronic and steady progression.205 This rule, however, has occasional exceptions, with patients showing either rapid deterioration124 or spontaneous improvement.137 Kuroda et al tried to depict factors of relevance to rapid clinical deterioration in HAM/TSP. Only patients who were young at the onset of disease experienced rapid clinical deterioration. Among laboratory parameters, depressed skin reactions to dinitrochlorobenzene and PPD (tuberculin test), depressed lymphoproliferative responses, and increased CSF levels of IgG were associated with rapid clinical deterioration.134

Recently, Araujo et al evaluated the progression profile of the neurologic disability of HAM/TSP in a series of 43 patients who had never received any previous immune therapy. The study suggested that the evolution of the neurologic disability in HAM/TSP occurs mainly during the first year of the disease and becomes relatively stable thereafter. They speculated that the variable therapeutic success rates observed in the literature could result from the timing in the beginning of the pharmacologic immunosuppression. It is also speculated that the therapeutic window in HAM/TSP lies within the first year of the disease.14

In a study by Nakagawa et al, patients with onset after the age of 15 years and no history of blood transfusion before the onset of the disease showed a shorter interval between the time of disease onset and that of inability to walk. Patients with onset before age 15 and without history of blood transfusion had slower progression of the disease. The interval time and the progression of the disease in patients with history of blood transfusion before onset of disease were in between those of the previous two groups. Patients whose age of onset was greater than 61 years experienced a faster progression than did those with earlier onset, regardless of the mode of HTLV-I transmission. Patients with low anti-HTLV-I antibody titers in the CSF had an older age of onset on average, milder clinical symptoms, and lesser increase of neopterin in the CSF than those in the high-titer subgroup, regardless of the mode of HTLV-I transmission. The clinical course of HAM/TSP may consist of an initial progressive phase, followed by a chronic phase. Some patients show acute/subacute onset and rapid progression.166

**Adult T-Cell Leukemia/Lymphoma**

In the 1970s, an epidemic of ATLL was detected in Japan. In 1980, two groups isolated the oncogenic virus HTLV-I.102, 192 The typical de-
scription of the clinical pattern involves prolonged fever, lymphadenopathy, hepatosplenomegaly, bone lesions with hypercalcemia, skin lesions, and a rapidly fatal course with poor response to chemotherapy. Early epidemiologic studies and the analysis of HTLV-I provirus integrated into neoplastic cell DNA demonstrated the association between ATLL and HTLV-I and established the relation between HTLV-I and ATLL. This is the description of the most common, acute leukemia form; however, the chronic type and smoldering types are also described with slower courses, more lymphomalike characteristics, and more extensive skin involvement.

In contrast with HAM/TSP, this disease occurs in older patients. The group more frequently affected is 50 to 60 years of age, with males predominating over females. In Japan, where HTLV-I is hyperendemic, studies have suggested a lifetime risk for ATLL of 2% to 4%. In Jamaica, Murphy estimated that lifetime risk of ATLL could be 4.0% for those infected before age 20. In other Caribbean countries, HTLV-I has also been associated with ATLL. Newly diagnosed ATLL cases are estimated at 500 per year in Japan, whereas in the United States and Europe, only a few cases are seen.

In Latin America, this association between HTLV-I and ATLL was recognized by Pombo in Brazil, Blank in Colombia, and in Argentina. At the National Institute of Cancer in Lima, Peru, 300 new cases of non-Hodgkin's lymphoma are detected each year, and at least 30 (10%) of these 300 new cases are associated with HTLV-I. The disease is usually seen in adults older than 50 years. In Jamaica, 55% of non-Hodgkin's lymphoma have HTLV-I infection versus 5.4% in the general population. Surprisingly, HTLV-I infection acquired through blood transfusion has not been associated with the development of ATLL, but this may reflect short follow-up periods rather than nonassociation.

**Strongyloides stercoralis Infection**

*Strongyloides stercoralis* is a soil-transmitted intestinal nematode that has been estimated to infect at least 60 million people worldwide. The uncomplicated intestinal form of the disease produces nonspecific abdominal symptoms with or without mild sporadic diarrhea; however, an autoinfective cycle may develop in a proportion of untreated cases. The autoinfective cycle usually results in low-grade, chronic infection in immunocompetent hosts.

In contrast to autoinfection, *S. stercoralis* may produce a life-threatening disseminated infection in immunocompromised hosts who are incapable of mounting an appropriate immune response against the parasite. An association of disseminated *S. stercoralis* infection with malignant tumors, severe malnutrition, acquired immunodeficiency syndrome (AIDS), corticosteroid therapy and renal transplantation has been well documented.

The results of previous studies carried out mostly in Japan and
Jamaica showed a significant association between HTLV-I infection and *S. stercoralis* infection.\textsuperscript{165, 201} None of these earlier studies contain sufficient clinical data to determine whether the high rate of parasite carriage had any influence on the clinical manifestations of HTLV-I-infected individuals; however, an association between disseminated *S. stercoralis* infection syndrome and concomitant HTLV-I infection has been suggested by several isolated case reports.\textsuperscript{56, 176, 188}

In recent publications, our group has described that 85.7% (18 of 21) of our patients with *S. stercoralis* hyperinfection have HTLV-I in the absence of other immunosuppressive diseases such as AIDS and cancer. The difference is statistically significant in comparison with a carefully matched control group (4.7%, 1/21) and a group with intestinal strongyloidiasis (10%, 6 of 62) (P<0.001).\textsuperscript{85} On the basis of these findings, we now recommend testing for HTLV-I infection in apparently immunocompetent patients who present with the syndrome of *S. stercoralis* hyperinfection.

There is report of a diminution of the therapeutic efficacy of thiabendazole among patients in Okinawa with concomitant *S. stercoralis*-HTLV-I infection.\textsuperscript{214} Recently, Terashima (submitted for publication) showed that the failure of the standard treatment against intestinal strongyloidiasis with thiabendazole or ivermectin is an important marker for HTLV-I infection. The above information suggests the usefulness of the performance of HTLV-I serology in patients failing standard therapy for *S. stercoralis* infection.

**Norwegian Scabies**

A rare clinical pattern of crusted scabies with generalized itching was observed among patients with various immunosuppressive diseases, Down syndrome, cancer, AIDS, and those undergoing chemotherapy.\textsuperscript{61, 187} Because of the massive numbers of mites present and delay in making an appropriate diagnosis, the disease has been nosocomially transmitted to healthy health care workers.\textsuperscript{220}

The association of Norwegian scabies with HTLV-I has been well documented.\textsuperscript{48, 53, 60} A selective immunosuppression against *Sarcoptes scabiei* has been described in patients with HTLV-I, ATLL, and TSP, and in asymptomatic seropositive patients in different locations. At Cayetano Heredia Hospital, in Lima, Peru, we have studied 10 patients with Norwegian scabies. Six had coinfection of HTLV-I (two had TSP).

**Coinfection with HIV**

Dual infection with HIV and HTLV-I was observed in Trinidad,\textsuperscript{18} Brazil,\textsuperscript{45} Peru,\textsuperscript{189} and the United States.\textsuperscript{191} In 552 Peruvian HIV-infected patients in 1989, 18.6% of the males and 5.3% of the females were HTLV-I coinfected. Coinfected males reported a significantly higher number of
new different sexual partners during the month prior to serum sample collection than those infected only with HIV ($P=0.002$). The effect of HTLV-I in the evolution of HIV infection is still largely unknown; two recent studies have suggested that patients with dual infections have a higher risk of developing AIDS.$^{18,31}$ In a prospective study of HIV-positive male IVDUs, those patients infected with both viruses were three times more likely to die from AIDS during the follow-up than those infected with HIV-I alone. In a Peruvian study conducted by the author (E. Gotuzzo), the mortality was 63.3% (38/60) in patients with HIV and 80% (12/15) in dually infected patients. Of 50 patients who died without receiving any antiretroviral treatment, the natural history of the disease produced a survival time of only 5.02 ± 3.27 months in patients with dual infection, shorter than that of patients with HIV alone (10.07 ± 4.42 months). In IVDUs with HIV infection, the cofactor of HTLV-I/II infection may adversely affect the clinical outcome of HIV infection. Similar data have been obtained in MSMs in Trinidad; however, they are in conflict with Schatcher in Brazil, who has presented information in which dual HIV-HTLV-I infection was not associated with worse prognosis or deeper immunodepression in comparison with HIV infection alone.$^{191}$

Recently in Bahia, Brazil, patients with tuberculosis and HTLV-I exhibited a worse clinical course and carried a poorer prognosis than tuberculosis patients without HTLV-I coinfection. Other diseases that are probably associated with HTLV-I include arthritis, Sjögren syndrome, polymyositis, and uveitis with or without thyroiditis.

HTLV-I is endemic in several Latin American countries and is becoming an emerging disease. Breast-feeding is an important risk factor for neonatal acquisition of HTLV-I. In the region, HTLV-I infection is considered a preventable STD. Unique and disseminated ethnic groups, mainly Quechua origin, African-Latin Americans, and Japanese descendants are more commonly infected. HAM/TSP, ATLL, and Strongyloides stercoralis hyperinfection are enhanced by concomitant HTLV-I infection. We recommend HTLV-I blood screening for blood donors in the region and family studies when one HTLV-I index case is detected.

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