Chronic Myelopathy Associated with Human T-Lymphotropic Virus Type I (HTLV-I)

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■ *Purpose:* To review the clinical, epidemiologic, immunologic, and virologic aspects of the chronic myelopathy associated with human T-cell leukemia/lymphoma virus type I (HTLV-I), currently called tropical spastic paraparesis/HTLV-I-associated myelopathy (TSP/HAM).

■ *Data Identification:* Studies done after 1985, when TSP/HAM was first recognized, were identified by a computer search using MEDLARS II and CANCERLIT. Additional information was acquired from personal files and bibliographies of existing literature.

■ *Study Selection:* A total of 400 articles, 90 book chapters, and 150 abstracts from meetings covering all aspects of HTLV-I and neurologic diseases were critically analyzed, and information from 250 publications was included.

■ *Results of Data Analysis:* TSP/HAM is present in most HTLV-I endemic areas, with a prevalence ranging from 5.1 to 128 per 100 000 inhabitants. Up to 20% of patients develop TSP/HAM after transfusion of HTLV-I contaminated blood. Pathologic characteristics indicate a chronic meningomyelitis. The clinical features consist of a chronic progressive spastic paraparesis or paraplegia, sphincter disturbances, and minimal sensory loss. Supraspinal and peripheral nerve involvement is sometimes observed. High titers of HTLV-I-specific antibodies are present in the serum and cerebrospinal fluid. The high level of humoral and cellular immunologic response and the association of TSP/HAM with other immunologic diseases suggest an immune-mediated process. Corticosteroids and immunosuppressor treatment usually result in only short-term improvement.

■ *Conclusion:* TSP/HAM is a common neurologic disease in many parts of the world. All patients with chronic progressive myelopathies should be tested for serum and cerebrospinal fluid HTLV-I-specific antibodies. Systematic screening of blood donors for HTLV-I is necessary to help prevent the dissemination of the virus and the occurrence of post-transfusional cases.

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Chronic progressive myelopathy is defined as a paraparesis or a paraplegia with gradual onset and variable degrees of sensory loss, without evidence of motor neuron involvement, spinal cord compression, or supramedullary disseminated lesions (1). During the last century, Charcot (2) and Erb (3) termed this syndrome primary lateral sclerosis according to the results of the autopsy. Subsequent autopsies series (4, 5), however, showed that the chronic progressive myelopathy group included a large variety of miscellaneous diseases, including tumors and infections as well as vascular and degenerative processes (including the entity primary lateral sclerosis). Paraclinical investigations such as evoked potentials, computed tomographic (CT) scans, and magnetic resonance imaging enable the clinician to make a precise diagnosis early in the course of the disease. Approximately 60% of chronic progressive myelopathy cases observed in Western countries are considered to be multiple sclerosis (6-8). In tropical areas (8-10), where multiple sclerosis is rare, chronic progressive myelopathy belongs to a subgroup of tropical myeloneuropathies referred to as endemic tropical spastic paraparesis (TSP) (11, 12). Tropical spastic paraparesis is a chronic spastic paraparesis found in tropical countries and is not associated with intoxication (such as cyanide consumption during droughts or lathyrism) or malnutrition. The disorder has received different names according to the origins of the patients (13-20). The clinical description and necropsy findings (13, 14) are quite similar, however, regardless of the patient's geographic origin. No cause was found, but an infectious agent was suspected.

In 1985 we first reported the high prevalence of serum antibodies against the human T-lymphotropic virus type I (HTLV-I) in patients with TSP living in Martinique (French West Indies) (21) and suggested that this virus might be neurotropic and might cause this disease. At that time, HTLV-I (22-24) (Figure 1), the first human exogenous retrovirus to be discovered, was known to be mainly endemic in the Caribbean area, Japan, and parts of Africa (25) and was considered to be the causative agent of adult T-cell leukemia/lymphoma (26, 27), an aggressive $CD4^+$ T-lymphoproliferative disorder. Soon thereafter, the association of HTLV-I and TSP was confirmed in Jamaica and Colombia (28). In 1986, in southern Japan, a similar association was documented, and this clinical entity was called HTLV-I-associated myelopathy (HAM) (29). In 1988 it was recognized that the HTLV-I-associated TSP and HAM were the same disease and the name TSP/HAM was retained (30).

In late 1985, soon after the link between HTLV-I and TSP was discovered, a report proposed (31) the possible involvement of an HTLV-I-related virus in multiple

Table 1. Epidemiologic Data on Tropical Spastic Paraparesis/HTLV-1-associated Myelopathy*

Origin of the Study (Reference)	Number of Cases	Male/ Female	Prevalence	Incidence	Previous Blood Transfusion	Familial Cases	Mean Age at Onset
	n		*n/100 000*	*n/100 000/y*	%		*y (range)*
Martinique (FWI) (91)	153 (100% HTLV-I +)	34/119	5.1	1.5	13	1.3	40 (21 to 48)
Japan (82)	560 (100% HTLV-I +)	145/415	8.6 (Kyushu)	0.04	20	8	43 (6 to 75)
Colombia (Tumaco) (12, 52)	55 (94.5% HTLV-I +)	26/29	100	6.3	0	0	46.5 (24 to 75)
Jamaica (93)	145 (63% HTLV-I +)	37/108	12	0.6	2	0	40 (14 to 78)
Seychelles (Mahé) (48)	21 (85% HTLV-I +)	7/14	128	2.3	0	23.8	43 (20 to 65)
Great Britain (74)	21 (90% HTLV-I +)	2/19			0	0	46 (20 to 68)
Chili (56, 122)	14 (100% HTLV-I +)	2/12			7	0	49
Zaïre (Lisala) (46)	25 (100% HTLV-I +)	9/16	50	3	0	48	31 (7 to 51)
France (73, 92)	21 (100% HTLV-I +)	7/14			23	4.7	42.6 (25 to 68)
South Africa (Natal) (64)	24 (100% HTLV-I +)	7/17			0	0	46.2 (27 to 70)

* References 73, 74, and 92 concern immigrant patients either from the West Indies (mostly Jamaica) or French West Indies (FWI), and French-speaking West African countries.

sclerosis. This report led to an intense debate in the neurologic and scientific community and to many efforts to provide additional evidence of HTLV-I infection in multiple sclerosis. The results of most of these studies were negative. Despite the sporadic detection of serologic and sometimes molecular HTLV-I-related markers in a few cases of multiple sclerosis, no compelling evidence currently exists to link HTLV-I with any form of this disease. This issue has been recently reviewed (32) and is not discussed here. In this paper we describe in detail all aspects of TSP/HAM and discuss its pathogenesis.

Epidemiology

This disease has usually been reported (12, 33) in high HTLV-I endemic areas: the Caribbean (21, 28, 34-36), southern Japan (29, 37-39), equatorial Africa (40-47), and the Seychelles (48). Endemic high prevalence foci of TSP/HAM have also been reported in Central (49) and South America (28, 50-59), Melanesia (60-62), and South Africa (63, 64). Sporadic cases have also been described in nonendemic HTLV-I areas such as the United States (65-70) and Europe (71-76), mainly in immigrants from an HTLV-I endemic area but also in some autochthons. In these latter cases, HTLV-I infection was most often acquired through contaminated blood transfusions or sexual intercourse with an HTLV-I-positive person from an endemic country. In a few cases the source of contamination was not discovered, and some authors have hypothesized the presence of small endemic foci in Western countries (73-76).

More than 1500 cases of TSP/HAM have been reported since 1985. Prevalence of the disease ranges from 8.6/100 000 inhabitants in Kyushu (Japan) to 128/100 000 in Mahé (Seychelles) (Table 1). The high prevalence of TSP/HAM observed in some geographical foci such as Tumaco (Colombia) (12, 54), Mahé (48), or Lisala (Zaïre) (46) reflects the high level of HTLV-I seropositivity rates among individual cities and locales within the endemic region (77-81) and sometimes the presence of risk factors. For example, in Colombia, TSP/HAM is observed primarily in an HTLV-I cluster along the Pacific coast (12, 74), whereas it is rarely found in the high plateau where seropositivity is low. In Japan, 69% of the TSP/HAM cases are from Kyushu and Okinawa. These two localities contain eight of the nine HTLV-I endemic prefectures of the country (77, 78).

The incidence of TSP/HAM is often difficult to estimate because of the limited number of neurologists in the endemic areas and the insidious onset of the disease. Estimates of the annual incidence range from 0.04/100 000 in Kyushu (82) to 3/100 000 in Lisala (46). In Japan the prevalence of TSP/HAM reaches 68.3/100 000 in HTLV-I seropositive persons (82) with an incidence of 3.1/100 000 HTLV-I infected persons/year. Assuming a lifetime of 75 years, the lifetime incidence is approximately 0.25% (83).

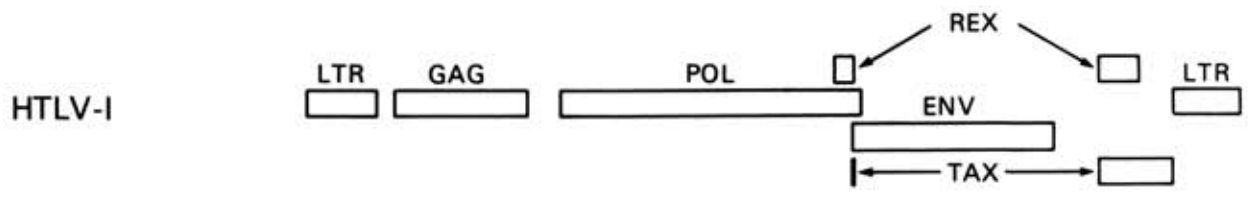

Figure 1. Schematic representation of the human T-lymphotropic virus type-1 genome. The HTLV-I genome contains, in addition to the viral promoters (long terminal repeats [LTR]) and to the known structural genes (*gag*, *pol*, and *env*), a unique region located between the *env* gene and the 3' long terminal repeat, which encodes for at least three proteins named $P40^{TAX}$, $P27^{REX}$, and $P21^{XIII}$. The $P40^{TAX}$ is a transcriptional transactivator for the HTLV-I long terminal repeat, as well as for cellular genes, such as interleukin-2, interleukin-2-receptor-α, granulocyte-macrophage colony-stimulating factors, and lymphotoxins. The $P27^{REX}$ is a post-transcriptional trans-regulator for HTLV-I expression. The function of $P21^{XIII}$ is currently unknown.

Table 2. Initial Symptoms and Handicap in Tropical Spastic Paraparesis/HTLV-1-associated Myopathy

Origin of the Study (Reference)	Number of Patients in Study	Initial Symptoms				Handicap			
		Weakness of Legs	Paraesthesia	Low Back Pain	Urinary Disturbances	Mean Duration of Illness	Bedridden	Walk with One or Two Crutches	Walk without Help
		← % →				y	← % →		
Martinique (35, 84, 91)	153	78	28	58	36	7	28	38	34
Colombia (52)	50	100	98	85	96	14 (1-30)	36	40	24
Seychelles (48)	21	80	80	42	47	10 (2-15)	38	38	24
Great Britain (74)	21	85	80	71	57	10 (1-30)	33	57	10
Japan (38)	90	90	?	?	?	15 (1-48)	15	49	36
France (73, 92)	21	76	9	19	42	6 (1-27)	24	52	24
South Africa (64)	24	100	45	49	78	< 2	50	41	9

Clinical Features

The disease occurs mainly in persons of African or Asian origin but can also be observed in whites. The mean age at onset of the disease is the fourth decade. Among African patients, a more precocious onset, in the third decade, has been observed (64). The onset of symptoms in persons younger than 20 years or older than 70 years is uncommon. Most studies indicate a female to male preponderance ranging from 1.5:1 in Japan (82) to 3.5:1 in Martinique (84).

The clinical picture of TSP/HAM (21, 85-96) is the same for patients of different geographic origins and is similar to the previous description of endemic TSP (11, 13, 14, 18). The onset is insidious without prodromata or triggering factors. Symptoms include stiffness or weakness in one or both legs, often associated with lumbar pain, and various sensory symptoms in the legs including numbness, burning, and "pins and needles" (Table 2). Urinary frequency, urgency, and penile impotence are common. The progression of the disease is variable but often severe. Ten years after contracting the disease, 30% of patients are bedridden, and 45% cannot walk unaided by crutches (35, 48, 53, 73, 74, 84, 87, 91, 92). Usually, the evolution is chronic, with progression over a number of years, finally reaching a plateau. A young age at onset has been associated with a more rapid progression (95). The evolution can be subacute (17, 46, 64), particularly in patients with post-transfusional cases (75, 97-100) and can lead to a complete paraplegia in less than 2 years. There have been a few reports of acute illness.

The clinical presentation (35, 85-94) is dominated by the presence of spastic paraparesis or paraplegia with signs of bilateral pyramidal tract lesions affecting the legs, manifested by increased knee reflexes, ankle clonus, and extensor plantar responses. Spasticity is moderate to severe. Motor weakness predominates in the proximal muscle groups. This muscle weakness and spasticity causes the slow, scissoring gait. In contrast with the paresthesias described by the patient, only minor sensory signs of involvement of the posterior columns and spinothalamic tract are found in the legs, consisting of decreased vibratory sensation and minor impairment of pinprick or light touch perception. A thoracic sensory level is uncommon. Brisk reflexes of the arms with a positive Hoffmann sign are frequent. Cognitive functions are normal. Cranial nerves are usually spared, but optic neuropathy has been described in a few cases (48, 63, 64, 92). Cerebellar signs limited to an intention tremor are reported in up to 20% of patients (48). Absent or depressed ankle jerk is occasionally reported in patients from tropical countries and is sometimes associated with a stocking-like hypesthesia to pinprick and light touch (53, 62, 90). Amyotrophy of the thighs and sometimes of the hands is rare (101, 103).

Familial cases represent less than 10% of the reported cases (57, 104) (*see* Table 1). In the Seychelles, 23% of the patients report previous cases of spastic paraparesis in their family (17) and, in Lisala, multiple cases of TSP/HAM were found in 10 out of 25 families studied (46), indicating the possibility of a genetic component. Conjugal cases have been reported in Tumaco (53) and in Martinique (91).

A few well-documented cases of TSP/HAM have been caused by HTLV-I-contaminated transfusions (75, 97-100), but a history of previous blood transfusion is found in 13% to 20% of patients in Japan (82, 105) and Martinique (84). In the first 2 years of blood supply screening in Japan, the number of reported patients with TSP/HAM appears to have decreased by 16% (82).

Similar chronic progressive myelopathy without detectable HTLV-I antibodies is frequently observed in countries endemic for HTLV-I or where classical TSP cases occur frequently (35, 106-108). Clinically, the reported patients with this condition are more frequently men, have the onset of their disease at a younger age, and have little or no sphincteric or sensory disturbances. Preliminary reports indicate that, in some instances, HTLV-I-related sequences could be detected in the DNA of the peripheral blood mononuclear cells (PBMCs) of some but not all of these patients, using the very sensitive technique of polymerase chain reaction (109, 110). The possibility that a latent HTLV-I infection could lead to disease in such patients is as yet unconfirmed.

A myelopathy clinically similar to TSP/HAM has been described in patients co-infected with human immunodeficiency virus-1 (HIV-1) and HTLV-I (42, 111-115). In these cases, the patients had no evidence of the acquired immunodeficiency syndrome (AIDS). Despite the lack of pathologic confirmation, an AIDS-related vacuolar myelopathy was unlikely in these patients be-

cause of the absence of clinical and laboratory evidence of significant immunosuppression and lack of other neurologic manifestations. It has been suggested that HIV-1 may increase the likelihood of developing TSP/HAM in a dually infected individual.

Radiologic and Electrophysiologic Studies

Results of myelography in patients with TSP/HAM are usually normal, with the exception of a few patients whose findings show a narrow cervical canal or minor cervical spondylosis (35, 73, 90). Magnetic resonance imaging of the spinal cord is either normal or displays atrophy of the thoracic spinal cord with a diffuse high signal on T2-weighted images (71, 73, 116). Nonspecific lesions of the brain are observed in 58% of patients on magnetic resonance imaging (Table 3, Figure 2). These consist of increased T2- and decreased T1-weighted sequences, either contiguous to the ventriculi or scattered throughout the deep cerebral white matter (65, 69, 71-74, 117-119). No clear correlation has been established between the lesions and the duration of illness or handicap (92, 118-120). According to one study (118), 64% of patients with TSP/HAM have discrete abnormalities on electroencephalograms. Visual-evoked potential displays an abnormal pattern in 30% of patients (65, 71, 73, 74, 92, 119, 120) (Table 3). Bilateral delayed latency of the P100 component is the most frequent abnormality. Studies of brain stem auditory evoked potentials show a slight delay of brain stem latency in 25% of patients (65, 71, 73, 74) (Table 3). Somatosensory evoked potentials are abnormal in the legs in 68% and in the arms in 34% of the patients (65, 71, 73, 74, 121-128) (Table 3). Motor-evoked potentials indicate an increase in the central conduction time of descending motor pyramidal pathways for both arms and legs (129-131). Urodynamic studies show a spastic bladder with an overactive detrusor and detrusor-urethral sphincter dyssynergia (132). Involvement of the peripheral nervous system, as assessed by nerve conduction velocities and needle electromyography, is found in 25% of patients with TSP/HAM (17, 65, 128, 133) (Table 3).

Systemic Signs and Association with Other Diseases

The association of the myelopathy with clinical or biological signs of involvement outside the nervous system was described in the early reports of TSP/HAM, where 5 of 22 patients had such signs (20, 21, 35, 134). Monoclonal gammapathy, cryoglobulinemia, necrotizing vasculitis, arthritis, polymyositis, inclusion myositis, recurrent conjunctivitis, uveitis, lymphocytic alveolitis, the sicca syndrome, diabetes, sarcoidosis, Vogt-Koyanagi-Harada disease, hepatitis, and various dermatologic changes are some of the disorders associated with TSP/HAM (20, 21, 35, 134-154). Most of the abnormalities are consistent with an alteration of immune processes and could be observed in an HTLV-I-seropositive person without any signs or symptoms of nervous system involvement; however, they seem to occur more frequently in patients with TSP/HAM. For example, asymptomatic lymphocytic alveolitis has been found in up to 80% of patients with TSP/HAM and ranges from 30% to 60% in the healthy HTLV-I seropositive carriers (136-140). Arthritis is found in 30% of Japanese patients with TSP/HAM compared with a few cases in the carriers (149-151).

Neuropathologic Features

Only a few postmortem reports of TSP/HAM have been published (103, 155-164). These reports agree with previous pathologic findings of classical TSP (13, 14). Macroscopically the brain appears normal, and the spinal cord is moderately to severely atrophied. The most prominent changes are a chronic inflammatory process of the spinal cord, most notably a meningomyelitis of the lower thoracic cord. Inflammatory changes are correlated with the duration of the disease, and significant inflammation is observed in cases of short duration. Inflammatory cells (B-cells, T-cells, macrophages, microglial cells) are present around the parenchymal vessels (mainly small veins and venules) and in the adjacent parenchyma. In cases of longer disease duration these inflammatory changes predominate in a perivascular localization and are accompanied by hyalinosis of blood vessels, meningeal fibrosis, and glial scars (161-163). Immunocytochemically, a predominance of $CD8^+$ cells associated with an overexpression of class I major histocompatibility complex (MHC) has been observed (159, 164). Parenchymal tissue damage involves both white and grey matter. The lesions are symmetric and usually occur along the tracts, mainly in the lateral

Table 3. Results of Electrophysiologic and Magnetic Resonance Imaging Studies*

Origin of the Study (Reference)	Visual Evoked Potentials	Somatosensory-evoked Potentials		Brain Stem Auditory-evoked Potentials	Electromyogram	Brain Magnetic Resonance Imaging
		Arms	Legs			
Japan (119, 120, 121, 125, 126)	13 (38)	7 (49)	33 (51)	5 (28)	0 (10)	13 (22)
Seychelles (48, 128)		7 (19)	11 (16)		13 (20)	
Chile (56, 122)	13 (22)	3 (22)	19 (22)	1 (22)	0 (15)	
Colombia (54)					5 (20)	
Europe (73, 74, 92)†						
USA (65)†						
Canada (69)†						
Total for Europe, USA, and Canada	26 (66)	24 (41)	26 (38)	25 (61)	7 (38)	37 (64)

* First number = the number of patients with abnormal results; numbers in parenthesis = the number of patients examined.
† Results shown are for the combination of studies (references 65, 69, 73, 74, and 92).

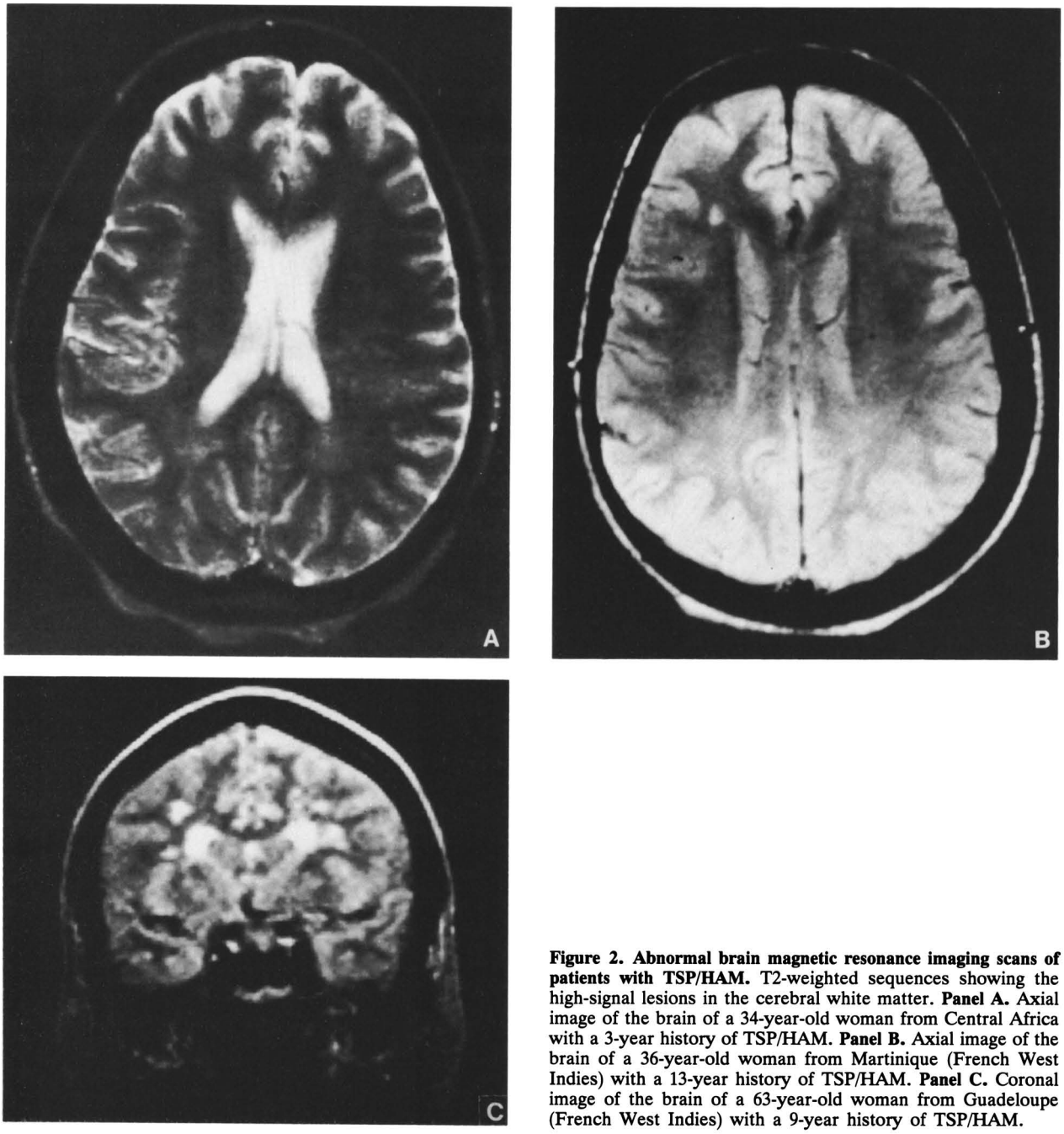

Figure 2. Abnormal brain magnetic resonance imaging scans of patients with TSP/HAM. T2-weighted sequences showing the high-signal lesions in the cerebral white matter. **Panel A.** Axial image of the brain of a 34-year-old woman from Central Africa with a 3-year history of TSP/HAM. **Panel B.** Axial image of the brain of a 36-year-old woman from Martinique (French West Indies) with a 13-year history of TSP/HAM. **Panel C.** Coronal image of the brain of a 63-year-old woman from Guadeloupe (French West Indies) with a 9-year history of TSP/HAM.

funiculi (157, 161). Both myelin and axons are destroyed. In presumably early lesions, however, the axons are relatively preserved. Leptomeninges and the spinal cord subarachnoid space display collagenous thickening and adhesion to the cord associated with lymphocyte infiltration. In the brain, perivascular mononuclear cell infiltration can be observed but is rarely associated with parenchymal tissue damage (103, 157-161). Only one report described HTLV-I-like particles in the spinal cord (165). A few sural nerve biopsies have been performed. In one case, axonal loss and demyelination with perivascular inflammatory cells localized mainly in the epineurium was seen (166). Inflammatory changes have also been reported in one patient infected with HTLV-I and HIV-1 (112). In other cases no inflammatory changes are found, and the principal abnormality is myelin breakdown with a globule formation (167).

Serologic Characteristics

By definition, HTLV-I specific antibodies are found in the serum and cerebrospinal fluid of patients with TSP/HAM (21, 28, 30, 35, 37, 168). Most of these antibodies are immunoglobulin IgG, but IgA and IgM have been reported in the sera and cerebrospinal fluid of some of these patients (169). Immunoglobulin G reactivities against *gag*-encoded proteins (*p19*, *p24*, and their precursor *pr* 53) and *env*-encoded proteins (*gp46* and *gp62*) are regularly detected in the sera and the

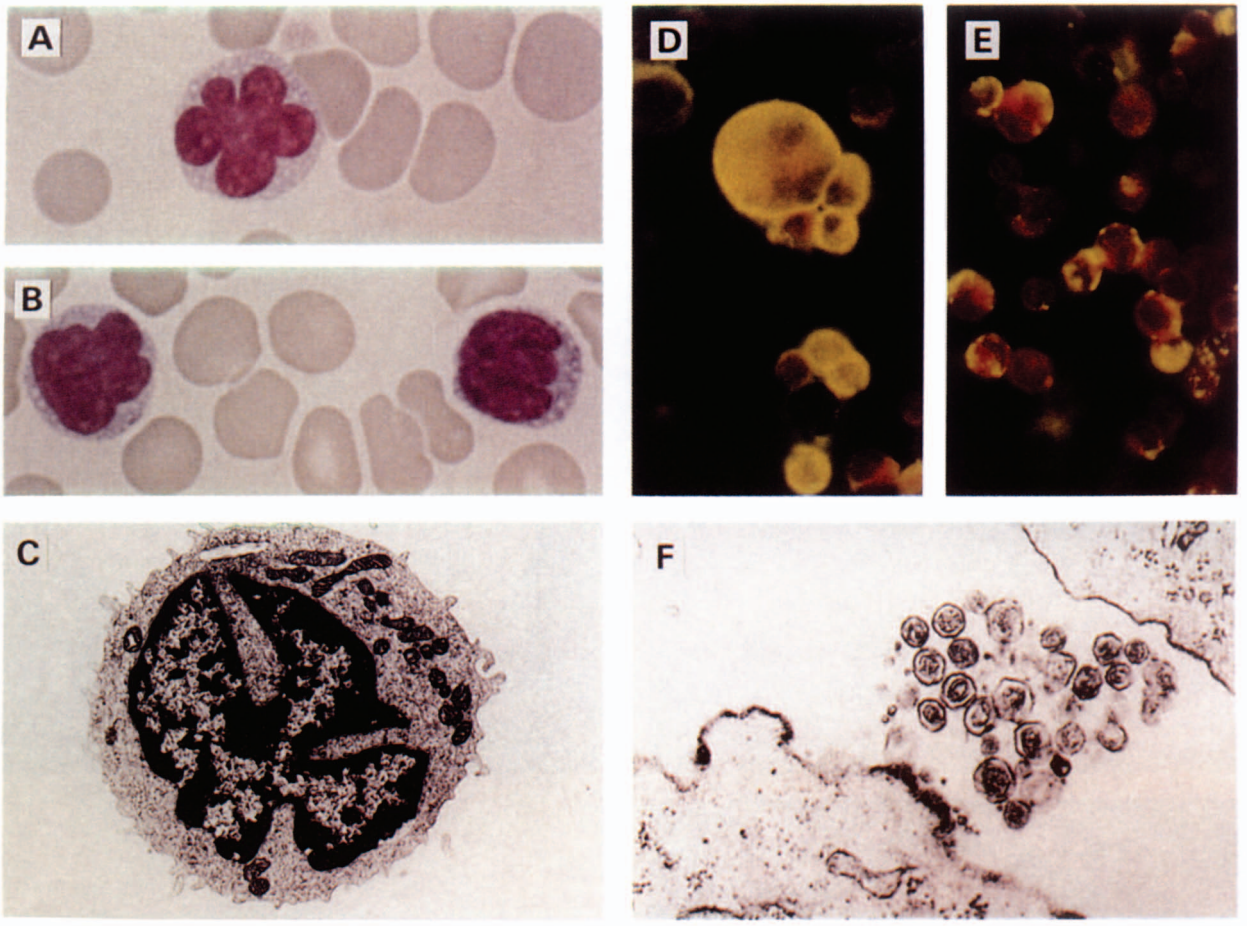

Figure 3. Atypical lymphocyte and viral expression in patients with TSP/HAM. Atypical lymphocyte with marked nuclear irregularities and convolutions. Such adult T-cell leukemia/lymphoma-like cells are present in a small percentage in peripheral blood mononuclear and cerebrospinal fluid cells of patients with TSP/HAM. **Panels A** and **B.** Optical microscopy (original magnification, × 500). **Panel C.** Electron microscopy (original magnification, × 19 000). **Panel D.** Immunofluorescence on a $CD4^+$, $CD25^+$ cell line established from cultured peripheral blood mononuclear cells of a patient with TSP/HAM using an anti-HTLV-I polyclonal serum; and **Panel E.** An anti-*p19* monoclonal antibody. The yellow cells express HTLV-I antigens. **Panel F.** Numerous C-type retroviral particles (HTLV-I) in extracellular spaces of cultured peripheral lymphocytes of a patient with TSP/HAM (original magnification, × 35 000).

cerebrospinal fluid (21, 30, 35, 37, 74, 170, 171). In most cases, antibody titers are significantly higher (170-172) in sera of patients with TSP/HAM than in sera from patients with ATL or from seropositive carriers. Nonsignificant spontaneous overtime fluctuation of HTLV-I antibodies has been reported, but a decrease of HTLV-I specific serum and sometimes of cerebrospinal fluid antibodies after some therapeutic trials has been observed (104). In the cerebrospinal fluid, HTLV-I specific antibodies are detected only at a clinically significant level in patients with TSP/HAM (87, 171, 173). This elevated HTLV-I antibody index is an indirect indication of antibody synthesis within the central nervous system. Intrathecal IgG synthesis, elevated IgG index and, intrablood-brain barrier IgG synthesis rate have been documented in most patients with an intact blood-brain barrier (170, 171, 173-175). Most patients with TSP/HAM have oligoclonal IgG bands in the cerebrospinal fluid. Some, but not all, are HTLV-I specific, directed against *p24* (174) or against the whole disrupted virus (170, 173, 174). These oligoclonal IgG bands are mainly present in the cerebrospinal fluid and can also be found in the serum (173). In two patients with a short clinical history, IgM oligoclonal IgG bands directed against HTLV-I were found (175). Treponema antibodies are also frequently present in patients from the tropics (17, 53, 176); this agent is no longer considered to have a role in the pathogenesis of TSP/HAM. Conflicting results have been reported concerning the presence and the specificity of *Borrelia burgdorferi* (17, 177) and Epstein-Barr virus (178) antibodies in the sera of patients with TSP/HAM. Elevation of cerebrospinal fluid neopterin (179) and of sera and cerebrospinal fluid interleukin-6 have been reported (180, 181). Circulating immune-complexes and auto-antibodies to brain endothelial cells have been observed in sera of patients with TSP/HAM (182).

Hematologic Findings and Cellular Immunology

The leukocyte count is within the normal range in most patients (35, 37, 183). On the peripheral blood smear, lymphoid cells with an abnormally shaped nucleus (indented, convoluted) are present in 1% to 20% of the total lymphoid cells (37, 183). Further, typical

ATL-like cells (flower cells) with foliated nuclei and hyperbasophilic cytoplasm are detectable in 1% to 5% of the total lymphocytes (183) (Figure 3). Such cells can occasionally be observed in few healthy HTLV-I-seropositive individuals (184).

The immunophenotypic analysis (183, 185-189) of the PBMCs indicate that most of the T cells are $CD4^+$ cells with a slight decrease of $CD8^+$ cells and, in most cases, an increase of the CD4/CD8 ratio. The percentage of B cells (CD19, CD20) is normal or low (1% to 10%) as is the percentage of monocytes (1% to 5%) (CD33). All studies indicate the presence of a high percentage of MHC class I (DP, DQ, DR) positive cells ranging from 15% to 60%. Double staining techniques (189) have shown the presence of an important population of activated large T cells bearing both the CD4 and activation markers. The levels of $CD25^+$ (interleukin-2-receptor) cells are also usually increased.

The circulating PBMCs of patients with TSP/HAM display a marked degree of spontaneous lymphocytic proliferation (189, 190). This phenomenon is also present, although to a lesser degree, in some healthy seropositive persons (191) and, as demonstrated by blocking experiments, seems to be mediated by the binding of interleukin-2 to its receptor (192). Interleukin-2 and soluble interleukin-2-receptors are elevated in sera of patients with TSP/HAM and seropositive carriers compared with healthy controls (192-194). Analyses of mRNA expression in fresh PBMCs revealed also that γ-interferon, tumor necrosis factor, and interleukin 1β transcripts are upregulated in patients with TSP/HAM and seropositive carriers when compared with normal controls (195).

High levels of circulating HTLV-I-specific cytotoxic T-lymphocytes have been reported (196-198) in blood and also in cerebrospinal fluid (199) in patients with TSP/HAM (but not in HTLV-I-seropositive individuals without neurologic impairment). These cytotoxic T-lymphocytes are both $CD8^+$ HLA class I end $CD4^+$ HLA class II restricted and recognize different HTLV-I gene products, especially some epitopes of the *tax*, the *rex*, and the *env* proteins.

In most cases, a mild pleocytosis ($< 50 \times 10^6$ leukocytes/L), predominantly lymphocytic, is present in the cerebrospinal fluid (35, 37, 38, 92). Adult T-cell leukemia/lymphoma-like cells may be found at a very low frequency. Activated T-lymphocytes are also found in the cerebrospinal fluid of patients with TSP/HAM (200).

In bronchoalveolar lavage, soluble interleukin-2-receptor levels are remarkably high (136-138) and correlate well with the number of T lymphocytes, $CD3^+$, and $CD4^+$. Bronchoalveolar lavage lymphocytes also show marked spontaneous proliferation when cultured in vitro, and specific HTLV-I IgA antibodies have been found in bronchoalveolar lavage fluid and sera of patients with TSP/HAM with pulmonary involvement.

In Japan (201), specific HLA haplotypes were found in patients with TSP/HAM as compared with patients with adult T-cell leukemia/lymphoma ATL or seropositive carriers. Such an HLA-disease association has not been confirmed in the West Indies (202). In the Japanese study (201) the in-vitro lymphocytes proliferation test revealed that PBMCs bearing "HAM-associated haplotypes" exhibited a definitely positive immune response of variable intensity to HTLV-I antigens; this contrasts with the absence or little response of PBMCs bearing the "adult T-cell leukemia/lymphoma-associated haplotypes."

Virologic Findings

Human T-lymphotropic virus type-1 proviral DNA can be easily detected in the fresh PBMCs' DNA of patients with TSP/HAM by using the polymerase chain reaction (65, 203, 204). Southern blot analyses have shown a polyclonal integration of HTLV-I (183, 205, 206) in most of the patients with TSP/HAM regardless of their geographical origin, the duration of their illness, or the level of their HTLV-I antibody titers. This HTLV-I polyclonal integration was estimated to be present in 3% to 15% of PBMCs (183). This high viral load in PBMCs has been confirmed by polymerase chain reaction analysis (207). The concordance between this result and the total number of abnormal lymphoid cells (5% to 20%), strengthens the hypothesis that most of the morphologically abnormal lymphoid cells may carry the HTLV-I provirus randomly integrated in their DNA. Moreover, recent polymerase chain reaction studies on fractioned uncultured PBMCs (208) have indicated that the virus is present primarily in $CD4^+$ cells, having been identified in up to 50% of these cells in some cases. The polyclonality of the peripheral T-cell population of these patients has been shown by molecular analysis using T-cell-receptor probes (206).

It is striking that despite this high viral load, no HTLV-I expression can be detected in fresh PBMCs by conventional techniques (209, 210). Recent reports (192, 211), however, have demonstrated that by polymerase chain reaction and reverse transcriptase in fresh PBMCs of patients with TSP/HAM, low levels of HTLV-I expression can be detected at least for the *tax/rex* regulatory genes. In-situ hybridization techniques indicate that such expression occurs in few cells (1 of every 100 to 5000 PBMCs) (211, 212). Integrated viral DNA has been detected by polymerase chain reaction in a high proportion of the bronchoalveolar lavage lymphocytes (213) but not in the adherent cells.

The coexistence of TSP/HAM and adult T-cell leukemia/lymphoma in the same patient has been rarely described (214-216). Southern blot analysis of PBMCs' DNA in one such patient demonstrated clonal integration of one or several HTLV-I proviral copies, affirming the diagnosis of adult T-cell leukemia/lymphoma. In a well-documented post-transfusional case of TSP/HAM (75), a transient clonal population of cells infected by HTLV-I was detected in the PBMCs' DNA only a few months after seroconversion.

Long-term T-cell lines producing HTLV-I virus (210, 217-221) can be established from cultured PBMCs, from cerebrospinal fluid cells, and from bronchoalveolar lavage lymphocytes of patients with TSP/HAM in the presence of exogenous interleukin-2. These are activated T cells: $CD2^+$, $CD3^+$, mostly $CD4^+$, but also rarely $CD8^+$ with a strong expression of HLA-DP and interleukin-2-receptor antigens. Most of these cell lines are clonal

and express HTLV-I antigens and release viral particles at a high level (218-220). After several months of culture they exhibit a clonal rearrangement pattern of T-cell-receptor β and γ genes and harbor one or multiple copies of clonally integrated HTLV-I viruses in their genomic DNA.

The viruses isolated from these cell lines are similar to the viruses isolated from adult T-cell leukemia/lymphoma and seropositive carrier-derived T-cell lines (210, 217-221). Moreover, molecular studies of these "TSP/HAM viruses" have not revealed major differences when compared with the "leukemogenic isolates" (220-235). This militates against the existence of a "neurotropic" strain in patients with TSP/HAM. Some slight nucleotide changes (mainly substitutions), however, have been observed in the long terminal repeat and in *env* genes of TSP/HAM isolates when compared with adult T-cell leukemia/lymphoma isolates (226-231). Studies are currently underway to determine whether or not the TSP/HAM and adult T-cell leukemia/lymphoma strains are functionally identical, if these slight differences reflect only intrastrain variability, or if they are due to the variation in the geographical origin of these patients (231, 235).

Therapeutic Aspects

The design of early therapeutic trials for patients with TSP/HAM was based on the hypothesis that the immune response plays a major role in disease progression. The first results from Japan indicated that corticosteroid treatment was beneficial to most patients with TSP/HAM when administered over a 6-month period (37, 38). The positive results were particularly evident for patients with a history of previous blood transfusion, patients with early cases, and for those presenting a low disability grade at study onset (38). No difference was seen, however, between the patients taking corticosteroids and those without therapy after a long-term follow-up (2 years) (38, 87); the results were the same no matter what type of corticosteroid or mode of administration was used. Improvement was rarely observed in patients with TSP/HAM from tropical countries (20, 35, 36, 53, 84), including those living in Europe (73, 74, 236). Plasmapheresis associated with corticosteroids and sometimes cyclophosphamide, as well as α-interferon therapy, also result in short-term improvement without long-term effects (86, 237-241). Short-term improvement has also been observed recently in patients receiving danazol therapy (242). Therapeutic trials using antibodies directed against the α-chain of the interleukin-2-receptor (anti-TAC) (192) are being evaluated.

The recent finding of an ongoing replication of HTLV-I in vivo (192, 211, 212), suggests that antiretroviral therapy could be effective. Both zidovudine (azidothymidine) and 2′3′-dideoxycytidine (ddC) have been shown to block the replication of HTLV-I in vitro (243). In an open trial, zidovudine, administered at a dose of 500 mg to 1 g/d, failed to benefit five patients with TSP/HAM. Paraclinical investigations, including virologic studies, remain stable during 6 months of therapy (244). In another zidovudine study of 10 patients (245), clinical improvement was noted over 24 weeks of therapy for five patients who had a low disability grade at the beginning of the study. However, four of these five regressed after withdrawal of the drug. These preliminary results demonstrate that zidovudine was well tolerated (244-246); trials currently underway determine the eventual benefit of such a therapeutic approach. Symptomatic therapy is nevertheless useful in decreasing the spasticity and painful paresthesias as well as in improving sphincter dysfunction.

Pathogenesis: Current Concepts and Hypothesis

Is the HTLV-I Retrovirus Associated with TSP/HAM A True Neurotropic Virus?

As noted above, molecular studies of HTLV-I strains isolated from patients with TSP/HAM have not revealed major differences when compared with adult T-cell leukemia/lymphoma isolates. However, slight differences, mainly nucleotide substitutions, have been found (226-231). It is known that for the murine leukemia virus model, a single mutation within the *env* gene region and sometimes the long terminal repeat may greatly influence the tissue tropism and growth characteristics of the viruses (247-249). Functional tests are needed to study the eventual differences between the long terminal repeat from TSP/HAM and adult T-cell leukemia/lymphoma isolates (250).

Does HTLV-I Infect and Replicate in Central Nervous System Cells In Vivo?

There is currently no clear-cut answer to this question, partially because the direct infectivity of HTLV-I for constituent cells of the central nervous system has not yet been determined. In-situ hybridization, done in very few cases of TSP/HAM autopsy material, has never been reported positive for HTLV-I RNA expression in any cell type of the central nervous system. HTLV-I proviral DNA has been detected by polymerase chain reaction in central nervous system tissues (251). The virus is not detected in peripheral blood monocytes or macrophages (208) and nothing is known about the central nervous system microglial cells of these patients. Adult and fetal human astrocytes and oligodendrocytes might possibly be infected in vitro (252-253).

Is TSP/HAM an Immunologically Mediated Disease?

The presence of circulating cytotoxic T-lymphocytes, $CD8^+$, HLA-I restricted, suggests that the cells can mediate the pathologic process (196-199). But are the cytotoxic T-lymphocytes, which seem to be mostly found in patients with TSP/HAM, only the consequence of the high viral load present in the PBMCs of these patients (183, 205-207)? If so, these cytotoxic T-lymphocytes could be directed only against the few HTLV-I expressing cells found within the large pool of $CD4^+$-infected cells. Conversely, the cytotoxic T-lymphocytes can also target and destroy other central nervous system cells not yet identified, which may express HTLV-I

antigens at a higher level. The existence of an HTLV-I specific oligoclonal B-cell response (IgG and IgM) occurring within the cerebrospinal fluid and a high proportion of cytotoxic T lymphocyte (up to 30% of the pleocytosis) found in the cerebrospinal fluid compartment is consistent with such a hypothesis. It is also worthwhile to note that the transfection of the *tax* gene into glial line cells induces class I HLA antigens on these cells (254).

Why Does an Asymptomatic HTLV-I Individual Develop TSP/HAM?

HTLV-I infection can be transmitted by breast feeding, sexual intercourse, intravenous drug use, or transfusion. After primary infection, most patients will seroconvert for HTLV-I and will remain asymptomatic, carrying the virus throughout their lifetimes. A few (< 5%) will develop adult T-cell leukemia/lymphoma, and a few others will develop TSP/HAM. The factors that determine the development of the disease (either leukemia or TSP/HAM) are unknown. Although differences in the genetic HLA background of patients with adult T-cell leukemia/lymphoma and TSP/HAM have been reported (201), several recent studies have noted their simultaneous occurrence in the same individual (214-216), militating against this hypothesis. Also, the report of TSP/HAM in a man, but not in his identical HTLV-I-seropositive twin, suggests that the development of this disease cannot be explained by the genetic factors alone (255). In the latter case, a high proviral HTLV-I load was found only in the twin who developed the TSP/HAM but not in his brother, who remains an asymptomatic carrier. The rapid development of TSP/HAM in some patients receiving HTLV-I contaminated platelets and sometimes red blood cells (75, 82, 83, 97-100) is remarkable and intriguing. The short period of incubation (in some cases only a few months) may be a result of the mode of infection, the high viral inoculum, co-factors transmitted by the same route, the host immunosuppression (present in a few cases), a booster effect in a previously HTLV-I infected individual, or other, as yet unidentified, risk factors. Finally, the possibility of neurotoxic viral gene products or metabolic alterations leading to the funicular degeneration need to be explored.

Conclusion

Tropical spastic paraparesis/HTLV-I is a frequent neurologic disease in most HTLV-I endemic areas. However, all patients with chronic progressive myelopathy must be tested for serum and cerebrospinal fluid HTLV-I specific antibodies to define the real-world magnitude of this recently recognized entity. Systematic screening of blood for HTLV-I is a necessary step in preventing the dissemination of the retrovirus and the occurrence of post-transfusional cases of TSP/HAM. Novel approaches to treatment, such as antiretroviral therapies, deserve systematic evaluations. Research directed to the elucidation of the pathogenesis of this condition should result in a better understanding of the mechanisms of retroviral infection in the human nervous system.

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References

1. **Paty DW, Blume WT, Brown WF, Jaatoul N, Kertesz A, McInnis W.** Chronic progressive myelopathy: investigation with CSF electrophoresis, evoked potentials, and CT scan. Ann Neurol. 1979;6: 419-24.
2. **Charcot JM.** Sclérose des cordons latéraux de la moelle épinière chez une femme hystérique atteinte de contracture permanente des quatre membres. Bull Soc Med Hop (Paris). 1865;2(Suppl. 2):24-42.
3. **Erb WA.** Über einen wenig bekannten spinalen symptomenkomplex. Klin Wochenschr. 1875;12:357-9.
4. **Marshall J.** Spastic paraplegia of middle age. Lancet. 1955;1:643-6.
5. **Ungar-Sargon JV, Lovelace RE, Brust JC.** Spastic paraplegia-paraparesis. J Neurol Sci. 1980;46:1-12.
6. **Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al.** New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol. 1983;13:227-31.
7. **Paty DW, Oger JJ, Kastrukoff LF, Hashimoto SA, Hooge JP, Eisen KA, et al.** MRI in the diagnosis of MS: a prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. Neurology. 1988;38:180-5.
8. **Poser M.** The epidemiology of multiple sclerosis in Africa and Asia. In: Chopra JS, Jagannathan K, Sawhney IM; eds. Advances in Neurology. Amsterdam: Elsevier Science Publishers; 1991:309-19.
9. **Kurtzke JF.** Geographic distribution of multiple sclerosis. An update with special reference to Europe and the Mediterranean region. Acta Neurol Scand. 1980;62:65-80.
10. **Kurtzke JF, Kurland LT.** The epidemiology of neurological disease. In: Baker AB, Baker LH; eds. Clinical Neurology. New York: Harper & Row; 1973:1-80.
11. **Román GC, Spencer PS, Schoenberg BS.** Tropical myeloneuropathies: the hidden endemias. Neurology. 1985;35:1158-70.
12. **Román GC.** The neuroepidemiology of tropical spastic paraparesis. Ann Neurol. 1988;23(Suppl. 7):113-20.
13. **Montgomery RD, Cruickshank EK, Robertson WB, McMenemey W.** Clinical and pathological observations on Jamaican neuropathy. Brain. 1964;87:425-62.
14. **Mani KS, Mani AJ, Montgomery RD.** A spastic paraplegic syndrome in South India. J Neurol Sci. 1969;9:179-99.
15. **Zaninovic V, Biojo R, Barreto P.** Paraparesia espastica del Pacifico. Colombia Medica. 1981;12:111-7.
16. **Kelly R, De Mol B.** Paraplegia in the islands of the Indian Ocean. Afr J Neurol Sci. 1982;1:5-7.
17. **Román GC, Spencer PS, Schoenberg BS, Hugon J, Ludolph A, Rodgers-Johnson P, et al.** Tropical spastic paraparesis in the Seychelles Islands: a clinical and case-control neuroepidemiologic study. Neurology. 1987;37:1323-8.
18. **Cosnett JE.** Unexplained spastic myelopathy: 41 cases in a non-European hospital. S Afr Med J. 1965;39:592-5.
19. **Wallace ID, Cosnett JE.** Unexplained spastic paraplegia. S Afr Med J. 1983;63:689-91.
20. **Vernant JC, Gessain A, Gout O, Maurs L, Buisson GG, Barin F, et al.** Paraparésies spastiques tropicales en Martinique. Haute prévalence d'anticorps HTLV-I. Presse Med. 1986;15:419-22.
21. **Gessain A, Barin F, Vernant JC, Gout O, Maurs L, Calender A, et al.** Antibodies to human T-lymphotropic virus type-1 in patients with tropical spastic paraparesis. Lancet. 1985;2:407-10.
22. **Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn AP, Minna JD, Gallo RC.** Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA. 1980;77:7415-9.
23. **Miyoshi I, Kubonishi I, Yoshimoto S, Akagi T, Ohtsuki Y, Shiraishi Y, et al.** Type C virus particles in a cord T-cell line derived by co-cultivating normal human cord leukocytes and human leukaemic T cells. Nature. 1981;294:770-1.

24. **Cann AJ, Chen IS.** Human T-cell leukemia virus types I and II. In: Fields BN, Knipe DM; eds. Virology. New York: Raven Press; 1990:1501-27.
25. **Blattner W.** Retroviruses. In: Evans AS; ed. Viral Infections of Humans. New York: Plenum Medical Book Co; 1989:545-92.
26. **Takatsuki K, Uchiyama T, Sagawa K, Yodoi J.** Adult T-cell leukemia in Japan. In: Senoo S, Takaku F, Irino S; eds. Topics in Hematology. Amsterdam: Excerpta Medica; 1977:73-7.
27. **Yoshida M, Seiki M, Yamaguchi K, Takatsuki K.** Monoclonal integration of human T-cell leukemia in all primary tumors of adult T-cell leukemia suggests causative role of human T-cell leukemia in the disease. Proc Natl Acad Sci USA. 1984;81:2534-7.
28. **Rodgers-Johnson P, Gajdusek DC, Morgan OS, Zaninovic V, Sarin PS, Graham DS.** HTLV-I and HTLV-III antibodies and tropical spastic paraparesis [Letter]. Lancet. 1985;2:1247-8.
29. **Osame M, Usuku K, Izumo S, Ijichi N, Amitani H, Igata A, et al.** HTLV-I associated myelopathy, a new clinical entity [Letter]. Lancet. 1986;1:1031-2.
30. **Román GC, Osame M.** Identity of HTLV-I-associated tropical spastic paraparesis and HTLV-I-associated myelopathy [Letter]. Lancet. 1988;1:651.
31. **Koprowski H, DeFreitas EC, Harper ME, Sandberg-Wollheim M, Sheremata WA, Robert-Guroff M, et al.** Multiple sclerosis and human T-cell lymphotropic retroviruses. Nature. 1985;318:154-60.
32. **Ehrlich GD, Glaser JB, Bryz-Gornia V, Maese BJ, Waldmann TA, Poiesz BJ, et al.** Multiple sclerosis, retroviruses, and PCR. Neurology. 1991;41:335-43.
33. **Molgaard CA, Eisenman PA, Ryden LA, Golbeck AL.** Neuroepidemiology of human T-lymphotrophic virus type-I-associated tropical spastic paraparesis. Neuroepidemiology. 1989;8:109-23.
34. **Bartholomew C, Cleghorn F, Charles W, Ratan P, Roberts L, Maharaj K, et al.** HTLV-1 and tropical spastic paraparesis [Letter]. Lancet. 1986;2:99-100.
35. **Vernant JC, Maurs L, Gessain A, Barin F, Gout O, Delaporte JM, et al.** Endemic tropical spastic paraparesis associated with human T-lymphotropic virus type I: a clinical and seroepidemiological study of 25 cases. Ann Neurol. 1987;21:123-30.
36. **Rodgers-Johnson P, Morgan OS, Mora C, Sarin P, Ceroni M, Piccardo P, et al.** The role of HTLV-I in tropical spastic paraparesis in Jamaica. Ann Neurol. 1988;23(Suppl.):S121-6.
37. **Osame M, Matsumoto M, Usuku K, Izumo S, Ijichi N, Amitani H, et al.** Chronic progressive myelopathy associated with elevated antibodies to human T-lymphotropic virus type 1 and adult T-cell leukemia-like cells. Ann Neurol. 1987;21:117-22.
38. **Osame M, Igata A, Matsumoto M, Kohka M, Usuku K, Izumo S.** HTLV-I associated myelopathy (HAM). Treatment trials, retrospective survey and clinical and laboratory findings. Hematol Rev. 1990;3:271-84.
39. **Shibasaki H, Tokudome S, Kuroda Y, Yanagawa T, Yoshihara M.** Prevalence of HTLV-I-associated myelopathy among HTLV-I carriers in Saga, Japan. Neuroepidemiology. 1989;8:124-7.
40. **Gessain A, Francis H, Sonan T, Giordano C, Akani F, Piquemal M, et al.** HTLV-I and tropical spastic paraparesis in Africa [Letter]. Lancet. 1986;2:698.
41. **Ryberg B, Blomberg J, Klasse PJ.** Tropical spastic paraparesis associated with human T-lymphotropic virus type 1 in an east African naturalised in Sweden. Br Med J. 1987;295:1380-1.
42. **Giordano C, Dumas M, Hugon J, Vallat JM, Sonan T, Piquemal M, et al.** Neuromyélopathies tropicales africaines: 61 cas étudiés en Côte d'Ivoire. Rev Neurol (Paris). 1988;144:578-85.
43. **de-Thé G, Giordano C, Gessain A, Howlett A, Sonan T, Akani F, et al.** Human retroviruses HTLV-I, HIV-1, and HIV-2 and neurological diseases in some equatorial areas of Africa. J Acquir Immune Defic Syndr. 1989;2:550-6.
44. **Delaporte E, Peeters M, Simoni M, Piot P.** HTLV-I infection in western equatorial Africa [Letter]. Lancet. 1989;2:1226.
45. **Hugon J, Vallat JM, Dumas M, Verdier M, Denis F, Akani F, et al.** Low prevalence of HTLV-1 antibodies in the serum of patients with tropical spastic paraplegia from the Ivory Coast [Letter]. J Neurol Neurosurg Psychiatry. 1990;53:269.
46. **Kayembe K, Goubau P, Desmyter J, Vlietinck R, Carton H.** A cluster of HTLV-1 associated tropical spastic paraparesis in Equateur (Zaïre): ethnic and familial distribution. J Neurol Neurosurg Psychiatry. 1990;53:4-10.
47. **Kazadi K, Garin B, Goussard B, Salaun JJ, de-Thé G.** Non-spastic paraparesis associated with HTLV-I [Letter]. Lancet. 1990;2:260.
48. **Román GC, Schoenberg BS, Madden DL, Sever J, Huggon J, Ludolph A, et al.** HTLV-I antibodies in patients with tropical spastic paraparesis from the Seychelles. Arch Neurol. 1987;44:605-7.
49. **Gracia F, Reeves WC, Levine PH, Cuevas M, Castillo L, Chavarría R, et al.** Human T-cell lymphotropic virus type I and neurologic disease in Panama, 1985 and 1986. Arch Neurol. 1990;47:634-9.
50. **Zaninovic V, Biojo R, Arango C, Barreto P.** El virus HTLV-I como posible causa de la paraparesia espastica del Pacifico. Colombia Medica. 1986;17:2-8.
51. **Zaninovic V, Arango C, Biojo R, Ramirez H, Borrero I.** Asociacion entre la infeccion por el virus linfocitotropico tipo I (HTLV-I) y la paraparesia espastica del Pacifico. Colombia Medica. 1986;17: 101-3.
52. **Román GC, Román LN, Spencer PS, Schoenberg BS.** Tropical spastic paraparesis: a neuroepidemiological study in Colombia. Ann Neurol. 1985;17:361-5.
53. **Román GC, Román LN.** Tropical spastic paraparesis. A clinical study of 50 patients from Tumaco (Colombia) and review of the worldwide features of the syndrome. J Neurol Sci. 1988;87:121-38.
54. **Zaninovic V, Arango C, Biojo R, Mora C, Rodgers-Johnson P, Concha M, et al.** Tropical spastic paraparesis in Colombia. Ann Neurol. 1988;23(Suppl. 1):S127-32.
55. **Johnson RT, Griffin DE, Arregui A, Mora C, Gibbs CJ Jr, Cuba JM, et al.** Spastic paraparesis and HTLV-I infection in Peru. Ann Neurol. 1988;23(Suppl. 1):S151-5.
56. **Cartier-Rovirosa L, Mora C, Araya F, Castillo J, Verdugo R, Miller MA, et al.** HTLV-I positive spastic paraparesis in a temperate zone [Letter]. Lancet. 1989;1:556-7.
57. **Salazar-Grueso EF, Holzer TJ, Gutierrez RA, Casey JM, Desai SM, Devare SG, et al.** Familial spastic paraparesis syndrome associated with HTLV-I infection. N Engl J Med. 1990;232:732-7.
58. **Takayanagui OM, Cantos JL, Jardim E.** Tropical spastic paraparesis in Brazil [Letter]. Lancet. 1991;2:309.
59. **Araujo A de Q, Ali A, Newell A, Dalgleish AG, Rudge P.** HTLV-I infection and neurological disease in Rio de Janeiro. J Neurol Neurosurg Psychiatry. 1992;55:153-5.
60. **Ajdukiewicz A, Yanagihara R, Garruto RM, Gajdusek DC, Alexander SS.** HTLV-I myeloneuropathy in the Solomon Islands [Letter]. N Engl J Med. 1989;321:615-6.
61. **Yanagihara R, Ajdukiewicz AB, Nerurkar VR, Garruto RM, Gajdusek DC.** Verification of HTLV-I infection in the Solomon Islands by virus isolation and gene amplification. Jpn J Cancer Res. 1991; 82:240-4.
62. **Yanagihara R, Ajdukiewicz AB, Garruto RM, Sharlow RE, Wa XY, Alemaena O, et al.** Human T-lymphotropic virus type I infection in the Solomon Islands. Am J Trop Med Hyg. 1991;44:122-30.
63. **Windsor IM, Bill PL, Bhigjee AI, Haribhai HC, Kelbe C, Hoffman M, et al.** HTLV-I-associated myelopathy in Natal [Letter]. S Afr Med J. 1988;74:370.
64. **Bhigjee AI, Kelbe C, Haribhai HC, Windsor IM, Hoffmann MH, Modi G, et al.** Myelopathy associated with human T-cell lymphotropic virus type I (HTLV-I) in Natal, South Africa. Brain. 1990; 113:1307-20.
65. **Bhagavati S, Ehrlich G, Kula R, Kwok S, Shinsky J, Udani V, et al.** Detection of human T-cell lymphoma/leukemia virus type 1 DNA and antigen in spinal fluid and blood of patients with chronic progressive myelopathy. N Engl J Med. 1988;318:1141-7.
66. **Saxton EH, Lee H, Swanson P, Chen IS, Ruland C, Chin E, et al.** Detection of human T-cell leukemia/lymphoma virus type I in a transfusion recipient with chronic myelopathy. Neurology. 1989; 39:841-4.
67. **Honig LS, Lipka J, Young KY, Weiss JH, Foung SK.** HTLV-I-associated myelopathy in a Californian: diagnosis by reactivity to a viral recombinant antigen. Neurology. 1991;41:448-50.
68. **McKendall RR, Oas J, Lairmore MD.** HTLV-I-associated myelopathy endemic in Texas-born residents and isolation of virus from CSF cells. Neurology. 1991;41:831-6.
69. **Power C, Weinshenker BG, Dekaban GA, Ebers GC, Traneis GS, Rice GP.** HTLV-I associated myelopathy in Canada. Can J Neurol Sci. 1989;16:330-5.
70. **Dixon PS, Bodner AJ, Okihiro M, Mibourne A, Diwan Am, Nakamura JM.** Human T-lymphotropic virus type I (HTLV-I) and tropical spastic paraparesis or HTLV-I-associated myelopathy in Hawaii. West J Med. 1990;152:261-7.
71. **Newton M, Cruickshank K, Miller D, Dalgleish A, Rudge P, Clayden S, et al.** Antibody to human T-lymphotropic virus type I in West-Indian-born UK residents with spastic paraparesis. Lancet. 1987;1:415-6.
72. **Tournier-Lasserve E, Gout O, Gessain A, Iba-Zizen MF, de Thé G, Lhermitte F, et al.** HTLV-I brain abnormalities on magnetic resonance imaging and relation with multiple sclerosis. [Letter]. Lancet. 1987;2:49-50.
73. **Gout O, Gessain A, Bolgert F, Saal F, Tournier-Lasserve E, Lasneret J, et al.** Chronic myelopathies associated with human T-lymphotropic virus type I. A clinical, serologic, and immunovirologic study of ten patients in France. Arch Neurol. 1989;46:255-60.
74. **Cruickshank JK, Rudge P, Dalgleish AG, Newton M, McLean BN, Barnard RO, et al.** Tropical spastic paraparesis and human T cell lymphotropic virus type 1 in the United Kingdom. Brain. 1989; 112:1057-90.
75. **Gout O, Baulac M, Gessain A, Semah F, Saal F, Périès J, et al.** Rapid development of myelopathy after HTLV-I infection acquired by transfusion during cardiac transplantation. N Engl J Med. 1990; 322:383-8.
76. **Annunziata P, Fanetti G, Giarratana M, Aucone AM, Guazzi GC.**

HTLV-I-associated spastic paraparesis in an Italian woman [Letter]. Lancet. 1987;2:1393-4.
77. **Hinuma Y, Komoda H, Chosa T, Kondo T, Kohakura M, Takenaka T, et al.** Antibodies to adult T-cell leukemia-virus-associated antigen (ATLA) in sera from patients with ATL and controls in Japan: a nation-wide sero-epidemiologic study. Int J Cancer. 1982;29: 631-5.
78. **Kajiyama W, Kashiwagi S.** Sero epidemiology of HTLV-I in Japan. In: Román G, Vernant JC, Osame M; eds. HTLV-I and the Nervous System. Neurology and Neurobiology. v 51. New York: Alan R. Liss; 1989;505-16.
79. **Murphy EL, Figueroa JP, Gibbs WN, Holding-Cobham M, Cranston B, Malley K, et al.** Human T-lymphotropic virus type I (HTLV-I) seroprevalence in Jamaica. Am J Epidemiol. 1991;133: 1114-24.
80. **Maloney EM, Murphy EL, Figueroa PJ, Gibbs WN, Cranston B, Hanchard B, et al.** Human T-lymphotropic virus type I (HTLV-I) seroprevalence in Jamaica. Am J Epidemiol. 1991;133:1125-34.
81. **Lavanchy D, Bovet P, Hollanda J, Shamlaye CF, Burezak JD, Lee H, et al.** High seroprevalence of HTLV-1 in the Seychelles [Letter]. Lancet. 1991;1:248-9.
82. **Osame M, Janssen R, Kubota H, Nishitani H, Igata A, Nagataki S, et al.** Nationwide survey of HTLV-I-associated myelopathy in Japan: association with blood transfusion. Ann Neurol. 1990;28: 50-6.
83. **Kaplan JE, Osame M, Kubota H, Igata A, Nishitani H, Maeda Y, et al.** The risk of development of HTLV-I-associated myelopathy/ tropical spastic paraparesis among persons infected with HTLV-I. J Acquir Immune Defic Syndr. 1990;3:1096-101.
84. **Vernant JC, Maurs L, Gout O, Buisson GG, Plumelle Y, Neisson-Vernant C, et al.** HTLV-I-associated tropical spastic paraparesis in Martinique: a reappraisal. Ann Neurol. 1988;23(Suppl. 1):S133-5.
85. **Shibasaki H, Endo C, Kuroda Y, Kakigi R, Oda K, Komine S.** Clinical picture of HTLV-I associated myelopathy. J Neurol Sci. 1988;87:15-24.
86. **Matsuo H, Nakamura T, Tsujihata M, Motomura M, Nagasato K, Nagataki S.** HTLV-I associated myelopathy in Nagasaki: clinical features and treatment of 21 cases. Jpn J Med. 1989;28:328-34.
87. **Osame M, Igata A, Matsumoto M.** HTLV-I associated myelopathy revisited. In: Román G, Vernant JC, Osame M; eds. HTLV-I and the Nervous System. Neurology and Biology. v. 51. New-York: Alan R Liss; 1989:213-23.
88. **Montgomery RD.** HTLV-I and tropical spastic paraparesis. 1. Clinical features, pathology and epidemiology. Trans R Soc Trop Med Hyg. 1989;83:724-8.
89. **Vernant JC, Román GC.** Mise au point: les paraplégies associées au virus HTLV-1. Rev Neurol (Paris). 1989;145:260-6.
90. **Vernant JC, Buisson GG, Ballance R, François MA, Madkoud O, Zavaro O.** HTLV-I associated paraplegias in Martinique. In: Román G, Vernant JC, Osame M; eds. HTLV-I and the Nervous System. Neurology and Neurobiology. v. 51. New York: Alan R. Liss; 1989:99-102.
91. **Buisson G, Bellance R, Francois MA, Grollier L, Bucher B, Vernant JC.** Inventaire des manifestations neurologiques associees au HTLV-1 en Martinique. Rétrovirus. 1990;6:72-4.
92. **Gout O, Gessain A, Baulac M, Fournel JJ, Cabanis EA, Dormont D, et al.** Myélopathies chroniques associées au virus HTLV-1 observées a l'Hôpital de la Pitié-Salpétrière. Role pathogène du HTLV-1 transmis par transfusion sanguine. Retrovirus. 1990;6:75-89.
93. **Rodgers-Johnson PEB, Ono SG, Asher DM, Gibbs CJ.** Tropical spastic paraparesis and HTLV-I myelopathy: clinical features and pathogenesis. In: Waksman BH; ed. Immunologic Mechanisms in Neurologic and Psychiatric Disease. New York: Raven Press; 1990:117-30.
94. **Román GC, Román LN, Osame M.** Human T lymphotropic virus type I neurotropism. In: Melnick JL; ed. Progress in Medical Virology. v. 37. New York: Karger; 1990:190-210.
95. **Kuroda Y, Fujiyama F, Nagumo F.** Analysis of factors of relevance to rapid clinical progression in HTLV-I-associated myelopathy. J Neurol Sci. 1991;105:61-6.
96. **Bucher B, Poupard JA, Vernant JC, DeFreitas EC.** Tropical neuromyelopathies and retroviruses: a review. Rev Infect Dis. 1990; 12:890-9.
97. **Sakai Y, Yao H, Sadoshima S, Fujishima M, Okochi K.** Development of HTLV-I associated myelopathy (HAM) in a seroconverted patient for antibody to HTLV-I [Letter]. J Neurol Neurosurg Psychiatry. 1989;52:1445.
98. **Desgranges C, Winter C, Delzant G.** Screening for HTLV-I [Letter]. Lancet. 1990;1:1517.
99. **Kurosawa M, Machii T, Kitani T, Tokumine Y, Kawa K, Maekawa L, et al.** HTLV-I associated myelopathy (HAM) after blood transfusion in a patient with CD2 + hairy cell leukemia. Am J Clin Pathol. 1991;95:72-6.
100. **Kaplan JE, Litchfield B, Rouault C, Lairmore MD, Luo CC, Williams L, et al.** HTLV-I-associated myelopathy associated with blood transfusion in the United States: epidemiologic and molecular evidence linking donor and recipient. Neurology. 1991;41: 192-7.
101. **Vernant JC, Buisson GG, Bellance R, François MA, Madkoud O, Zavaro O.** Pseudo-amyotrophic lateral sclerosis, peripheral neuropathy and chronic polyradiculoneuritis in patients with HTLV-I associated paraplegia. In: Román G, Vernant JC, Osame M; eds. HTLV-I and the Nervous System. Neurology and Neurobiology. v. 51. New York: Alan R. Liss; 1989:361-5.
102. **Arimura K, Nakashima H, Matsumoto W, Ohsako H, Hashiguchi K, Higuchi I, et al.** HTLV-I associated myelopathy (HAM) presenting with ALS-like features. In: Román G, Vernant JC, Osame M; eds. HTLV-I and the Nervous System. Neurology and Neurobiology. v. 51. New York: Alan R. Liss; 1989;367-70.
103. **Kuroda Y, Sugihara H.** Autopsy report of HTLV-I-associated myelopathy presenting with ALS-like manifestations. J Neurol Sci. 1991;106:199-205.
104. **Miyai I, Saida T, Fujita M, Kitahara Y, Hirono N.** Familial cases of HTLV-I-associated myelopathy. Ann Neurol. 1987;22:601-5.
105. **Osame M, Izumo S, Igata A, Matsumoto M, Matsumoto T, Sonoda S, et al.** Blood transfusion and HTLV-I associated myelopathy [Letter]. Lancet. 1986;2:104-5.
106. **Itoyama Y, Minato S, Goto I.** HTLV-I associated myelopathy (HAM) and seronegative spastic spinal paraparesis (SSP). In: HTLV-I and the Nervous System. Román G, Vernant JC, Osame M; eds. Neurology and Neurobiology. v. 51. New York: Alan R. Liss; 1989:209-12.
107. **Dagleish AG, Richardson JH, Newman PK, Newwell A, Rangan G, Mani K.** HTLV-I, tropical spastic paraparesis and other neurological diseases in south India. In: Blattner WA; ed. Human Retrovirology: HTLV. New York: Raven Press; 1990:245-50.
108. **Richardson JH, Newell AL, Newman PK, Mani KS, Rangan G, Dagleish AG.** HTLV-I and neurological disease in south India [Letter]. Lancet. 1989;1:1079.
109. **d'Auriol L, Vernant JC, Ouka M, Nerienet E, Buisson G, Neisson-Vernant C, et al.** Diagnosis of HTLV-I infected seronegative neurological patients by polymerase chain reaction amplification in Martinique. Nouv Rev Fr Hematol. 1990;32:113-6.
110. **Haettich B, Desgranges C, Veillon L, Prier A, Kaplan G.** Intérêt de l'amplification génique (polymerase chain reaction) dans l'identification des manifestations neurologiques associées au HTLV-1 [Letter]. Presse Med. 1991;20:661.
111. **Hugon J, Dumas M, Vallat JM, Denis F, Piquemal M, Giordano C, Barin F.** Spastic paraparesis and dual exposure to human T-lymphotropic virus type 1 and human T-lymphotropic virus type IV [Letter]. Ann Intern Med. 1987;11:111.
112. **McArthur JC, Griffin JW, Cornblath DR, Griffin DE, Tesoriero T, Kunel R, et al.** Steroid-responsive myeloneuropathy in a man dually infected with HIV-1 and HTLV-I. Neurology. 1990;40:938-44.
113. **Koppel BS, Williams S, Daras M, DePietro D, Kaplan M, Coronesi M, et al.** Myelopathy in patients with the acquired immunodeficiency syndrome coinfected with human T-lymphotropic virus type 1 [Abstract]. Ann Neurol. 1990;28:252.
114. **Berger JR, Svenningsson A, Raffanti S, Resnick L.** Tropical spastic paraparesis-like illness occurring in a patient dually infected with HIV-1 and HTLV-II. Neurology. 1991;41:85-7.
115. **Berger JR, Raffanti S, Svenningsson A, McCarthy M, Snodgrass S, Resnick L.** The role of HTLV in HIV-1 neurologic disease. Neurology. 1991;41:197-202.
116. **Kermode AG, Rudge P, Thompson AJ, du Boulay EP, McDonald WI.** MRI of thoracic cord in tropical spastic paraparesis [Letter]. J Neurol Neurosurg Psychiatry. 1990;53:1110-1.
117. **Mattson DH, McFarlin DE, Mona C, Zaninovic V.** Central-nervous-system lesions detected by magnetic resonance imaging in an HTLV-I antibody positive symptomless individual [Letter]. Lancet. 1987;2:49.
118. **Kira J, Minato S, Itoyama Y, Goto I, Kato M, Hasuo K.** Leukoencephalopathy in HTLV-I-associated myelopathy: MRI and EEG data. J Neurol Sci. 1988;87:221-32.
119. **Furakawa Y, Osama M, Une F.** Magnetic resonance imaging (MRI) abnormalities. In: Román G, Vernant JC, Osame M, eds. HTLV-I and the Nervous System. Neurology and Neurobiology. v. 51. New York: Alan R. Liss; 1989:393-6.
120. **Kira J, Fujihara K, Itoyama Y, Goto I, Hasuo K.** Leukoencephalopathy in HTLV-I-associated myelopathy/tropical spastic paraparesis: MRI analysis and a two year follow-up study after corticosteroid therapy. J Neurol Sci. 1991;106:41-9.
121. **Kakigi R, Shibasaki H, Kurodo Y, Endo C, Oda K, Ikeda A, et al.** Multimodality evoked potentials in HTLV-I associated myelopathy. J Neurol Neurosurg Psychiatry. 1988;51:1094-6.
122. **Castillo JL, Cartier L, Araya F, Verdugo R, Mora C, Gibbs C.** Evoked potential abnormalities in progressive spastic paraparesis associated with HTLV-I. Acta Neurol Scand. 1991;83:151-4.
123. **Shibasaki H.** Notes on the pathophysiology of HTLV-I associated myelopathy based on clinical and electrophysiological observations. In: Román G, Vernant JC, Osame M; eds. HTLV-I and the

Nervous System. Neurology and Neurobiology. v. 51. New York: Alan R. Liss; 1989:227-32.
124. **Hugon J, Giordano C, Dumas M, Denis F, Vallat JM, Barin F, et al.** Evoqued motor potentials in patients with tropical spastic paraparesis. In: Román G, Vernant JC, Osame M; eds. HTLV-I and the Nervous System. Neurology and Neurobiology. v. 51. New York: Alan R. Liss; 1989:233-8.
125. **Arimura K, Rosales LR, Osame M, Igata A.** Clinical electrophysiologic studies of HTLV-I-associated myelopathy. Arch Neurol. 1987;44:609-12.
126. **Arimua K, Arimura Y, Yonenaga Y, Rosales R, Osame M.** Clinical electrophysiologic findings in patients with HTLV-I associated myelopathy. In: Román G, Vernant JC, Osame M, eds. HTLV-I and the Nervous System. Neurology and Neurobiology. v. 51. New York: Alan R. Liss; 1989:245-50.
127. **Arimura Y, Arimura K, Osame M, Igata A.** Neuro-ophthalmological abnormalities in HTLV-I associated myelopathy. Neuro-ophthalmology. 1987;7:243-8.
128. **Ludolph AC, Hugon J, Román GC, Spencer PS, Schoenberg BS.** A clinical neurophysiologic study of tropical spastic paraparesis. Muscle Nerve. 1988;2:392-7.
129. **Ugawa Y, Kohara N, Shimpo T, Mannen T.** Central motor and sensory conduction in adrenoleukomyelopathy, cerebrotendinous xanthomatosis, HTLV-I associated myelopathy and tabes dorsalis. J Neurol Neurosurg Psychiatry. 1988;51:1069-74.
130. **Tomita I, Motomura M, Nagasato K, Shibayana K, Tsujihata M, Nagataki S.** Central motor conduction time (CCT) in patients with human T lymphotropic virus type I associated myelopathy (HAM). In: Román G, Vernant JC, Osame M; eds. HTLV-I and the Nervous System. Neurology and Neurobiology. v. 51. New York: Alan R. Liss; 1989:239-44.
131. **Waddy H, Claus D, Murray NMF, Rudge P.** Central motor conduction studies in tropical spastic paraparesis (TSP) [Abstract]. Electroencephalogr Clin Neurophysiol. 1990;75(Suppl.):159-60.
132. **Hiyoshi T, Osame M, Moritoyo T, Takahashi K, Nakamura R, Kubota R, et al.** Cystometric analysis of the urinary function of HTLV-1 associated myelopathy; a preliminary report. Acta Med Univ Kagoshima. 1987;29:19-27.
133. **Barkhaus PE, Morgan O.** Jamaican neuropathy; an electrophysiological study. Muscle Nerve. 1988;11:380-5.
134. **Vernant JC, Buisson GG, Sobesky G, Arfi S, Gervaise G, Román GC.** Can HTLV-I lead to immunological disease? [Letter]. Lancet. 1987;2:404.
135. **Coleman RJ, Zuckerman M, Swash M.** HTLV-1 infection: the clinical spectrum widens [Letter]. J Neurol Neurosurg Psychiatry. 1991;54:371.
136. **Sugimoto M, Nakashima H, Watanabe S, Uyama E, Tanaka F, Ando M, et al.** T-lymphocyte alveolitis in HTLV-I associated meylopathy [Letter]. Lancet. 1987;2:1220.
137. **Sugimoto M, Nakashima H, Kawano O, Ando M, Araki S.** Bronchoalveolar T-lymphocytosis in HTLV-I associated myelopathy [Letter]. Chest. 1989;95:708.
138. **Sugimoto M, Nakashima H, Matsumoto M, Uyama E, Ando M, Araki S.** Pulmonary involvement in patients with HTLV-I associated myelopathy: increased soluble IL-2 receptors in bronchoalveolar lavage fluid. Am Rev Respir Dis. 1989;139:1329-35.
139. **Couderc LJ, Caubarrere I, Venet A, Magdeleine J, Jouanelle A, Danon F, et al.** Bronchoalveolar lymphocytosis in patients with tropical spastic paraparesis associated with human T-cell lymphotropic virus type I (HTLV-I). Ann Intern Med. 1988;109:625-8.
140. **Couderc LJ, Caubarrere I, Venet A, Magdeline J, Jouanelle A, Danon F, et al.** Alvéolite lymphocytaire et myélopathie associée au virus HTLV-I. Retrovirus. 1990;3:109-13.
141. **Mora CA, Garruto RM, Brown P, Guiroy D, Morgan OS, Rodgers-Johnson P, et al.** Seroprevalence of antibodies to HTLV-I in patients with chronic neurological disorders other than tropical spastic paraparesis. Ann Neurol. 1988;23(Suppl. 1):S192-5.
142. **Morgan OS, Rodgers-Johnson P, Mora C, Char G.** HTLV-I and polymyositis in Jamaica. Lancet. 1989;2:1184-7.
143. **Goudreau G, Karpati G, Carpenter S.** Inflammatory myopathy in association with chronic myelopathy in HTLV-I seropositive patients [Abstract]. Neurology. 1988;38(Suppl. 1):206.
144. **Francis DA, Hughes RA.** Polymyositis and HTLV-I antibodies [Letter]. Ann Neurol. 1989;25:311.
145. **Evans BK, Gore I, Harrell LE, Arnold J, Oh SJ.** HTLV-I associated myelopathy and polymyositis in US native. Neurology. 1989; 39:1572-5.
146. **Tarras S, Sheramata W, Snodgren S, Ayyar DR.** Polymyositis and chronic myelopathy associated with presence of serum and cerebrospinal fluid antibody to HTLV-I. In: Román G, Vernant JC, Osame M; eds. HTLV-I and the Nervous System. Neurology and Neurobiology. v. 51. New York: Alan R. Liss; 1989:435-41.
147. **Masson C, Chaunu MP, Hénin D, Masson M, Cambier J.** Myélopathie, polymyosite et manifestations systémiques associées au virus HTLV-I. Rev Neurol (Paris). 1989;145:838-41.
148. **Bowness P, Davies KA, Tosswill J, Bunn CC, MacAlpine L, Weber JN, et al.** Autoimmune disease and HTLV-I infection. Br J Rheumatol. 1991;30:141-3.
149. **Nishioka K, Maruyama I, Sato K, Kitajima I, Nakajima Y, Osame M.** Chronic inflammatory arthropathy associated with HTLV-I [Letter]. Lancet. 1989;1:441.
150. **Kitajima I, Maruyama I, Maruyama Y, Ijichi S, Eiraku N, Mimura Y, et al.** Polyarthritis in human T lymphotropic virus type I-associated myelopathy [Letter]. Arthritis Rheum. 1989;32:1342-4.
151. **Ijichi S, Matsuda T, Maruyama I, Izumihara T, Kojima K, Niimura T, et al.** Arthritis in a human T lymphotropic virus type I (HTLV-1) carrier. Ann Rheum Dis. 1990;49:718-21.
152. **Herskovitz S, Sparr SA, Lairmore MD.** Limb-girdle syndrome and autonomic failure associated with human T lymphotrophic virus type I infection [Abstract]. Ann Neurol. 1990;28:279.
153. Case record 36-1989. N Engl J Med. 1989;321:663-75.
154. **Tagegoshi K, Nakanuma Y, Tsukuda K, Okuda K.** Human T-lymphotropic virus type-I-associated myelopathy and primary sclerosing cholangitis. J Clin Gastroenterol. 1991;13:202-4.
155. **Akizuki S, Nakazato O, Higuchi Y, Tanabe K, Setoguchi M, Yoshida S, et al.** Necropsy findings in HTLV-1 associated myelopathy [Letter]. Lancet. 1987;1:156-7.
156. **Piccardo P, Ceroni M, Rodgers-Johnson P, Mora C, Asher DM, Char G, et al.** Pathological and immunological observations on tropical spastic paraparesis in patients from Jamaica. Ann Neurol. 1988;23(Suppl. 1):S156-60.
157. **Akizuki S, Setoguchi M, Nakazato O, Yoshida S, Higuchi Y, Yamamoto S, et al.** An autopsy case of human T-l;ymphotropic virus type I-associated myelopathy. Hum Pathol. 1988;19:988-90.
158. **Akizuki S, Yoshida S, Setoguchi M, Higuchi Y, Yamamoto S, Nakazato O, et al.** The neuropathology of human T-lymphotropic virus type 1-associated myelopathy. In: Román G, Vernant JC, Osame M; eds. HTLV-I and the Nervous System. Neurology and Neurobiology. v. 51. New York: Alan R. Liss; 1989:253-60.
159. **Moore GR, Traugott U, Scheinberg LC, Raine CS.** Tropical spastic paraparesis: a model of virus-induced, cytotoxic T-cell-mediated demyelination? Ann Neurol. 1989;26:523-30.
160. **Liberski PP, Rodgers-Johnson P, Yanagihara R, Gibbs CH Jr, Gajudsek DC.** Cambios neuropatologicos ultraestructurales de una encefalomieloneuropatia por retrovirus. Retrovirus humanos: HTLV-1 paraparesia espastica y Linfomas V. Zaninovic; ed. CaliFeriva Editores; 1989:133-46.
161. **Iwasaki Y.** Pathology of chronic myelopathy associated with HTLV-1 infection (HAM/TSP). J Neurol Sci. 1990;96:103-23.
162. **Ohame E, Horikawa Y, Shimizu T, Morita T, Nemoto K, Tanaka H, et al.** Demyelination and remyelination in spinal cord lesions of human lymphotropic virus type I-associated myelopathy. Acta Neuropathol. 1990;81:78-83.
163. **Sasaki S, Komori T, Maruyama S, Takeishi M, Iwasaki Y.** An autopsy case of human T lymphotropic virus type I-associated myelopathy (HAM) with a duration of 28 years. Acta Neuropathol. 1990;81:219-22.
164. **Bhigjee AI, Wiley CA, Wachsman W, Amenomori T, Pirie D, Bill PL, Windsor I.** HTLV-I-associated myelopathy: clinicopathologic correlation with localization of provirus to spinal cord. Neurology. 1991;41:1990-2.
165. **Liberski PP, Rodgers-Johnson P, Char G, Piccardo P, Gibbs CJ Jr, Gajdusek DC.** HTLV-I-like viral particles in spinal cord cells in Jamaican tropical spastic paraparesis. Ann Neurol. 1988;23(Suppl. 1):S185-7.
166. **Said G, Goulon-Groean C, Lacroix C, Fève A, Descamps H, Fouchard M.** Inflammatory lesions of peripheral nerve in a patient with human T-lymphotropic virus type 1-associated myelopathy. Ann Neurol. 1988;24:275-7.
167. **Sugimura K, Takahashi A, Watanabe M, Mano K, Watanabe H.** Demyelinating changes in sural nerve biopsy of patients with HTLV-I-associated myelopathy. Neurology. 1990;40:1263-6.
168. **DeFreitas E, Wroblewska Z, Maul G, Sheremata W, Ferrante P, Lavi E, et al.** HTLV-I infection of cerebrospinal fluid T cells from patients with chronic neurologic disease. AIDS Res Hum Retroviruses. 1987;3:19-32.
169. **Nagasato K, Nakamura T, Ohishi K, Shibayama K, Motomura M, Ichinose K, et al.** Active production of anti-human T-lymphotropic virus type 1 (HTLV-1) IgM antibody in HTLV-1-associated myelopathy. J Neuroimmunol. 1991;32:105-9.
170. **Cerroni M, Piccardo P, Rodgers-Johnson P, Mora C, Asher DM, Gajdusek DC, et al.** Intrathecal synthesis of IgG antibodies to HTLV-I supports an etiological role for HTLV-I in tropical spastic paraparesis. Ann Neurol. 1988;23(Suppl. 1):S188-91.
171. **Gessain A, Caudie C, Gout O, Vernant JC, Maurs L, Giordano C, et al.** Intrathecal synthesis of antibodies to human T lymphotropic virus type I and the presence of IgG oligoclonal bands in the cerebrospinal fluid of patients with endemic tropical spastic paraparesis. J Infect Dis. 1988;157:1226-34.
172. **Dalgleish A, Richardson J, Matutes E, Cruickshank K, Newell A, Sinclair A, et al.** HTLV-I infection in tropical spastic paraparesis:

lymphocyte culture and serologic response. AIDS Res Hum Retroviruses. 1988;4:475-85.
173. **Link H, Cruz M, Gessain A, Gout O, de-Thé G, Kam-Hansen S.** Chronic progressive myelopathy associated with HTLV-I: oligoclonal IgG and anti-HTLV-I IgG antibodies in cerebrospinal fluid and serum. Neurology. 1989;39:1566-72.
174. **Grimaldi LM, Roos RP, Devare SG, Casey JM, Maruo Y, Hamada T, et al.** HTLV-I associated myelopathy: oligoclonal immunoglobulin G bands contain anti-HTLV-I p24 antibody. Ann Neurol. 1988;24:727-31.
175. **McLean BN, Rudge P, Thompson EJ.** Viral specific IgG and IgM antibodies in the CSF of patients with tropical spastic paraparesis. J Neurol. 1989;236:351-2.
176. **Rodgers-Johnson PE, Garruto RM, Gajdusek DC.** Tropical myeloneuropathies—a new aetiology. Trends Neurosci. 1988;11:526-32.
177. **Bucher B, Poupard JA, Parra JP, Vernant JC, Buisson G, Koprowski J, et al.** *Borrelia burgdorferi* and tropical spastic paraparesis [Letter]. Lancet. 1990;336:1135.
178. **Goubau P, Kazadi K, De Castro Costa CM, Carton H, Desmyter J.** Absence of Epstein-Barr virus activation in HTLV-I-associated tropical spastic paraparesis. Neurology. 1991;41:1158-9.
179. **Nomoto M, Utatsu Y, Soejima Y, Osame M.** Neopterin in cerebrospinal fluid: a useful marker for diagnosis of HTLV-I-associated myelopathy/tropical spastic paraparesis [Letter]. Neurology. 1991; 41:457.
180. **Nishimoto N, Yoshizaki K, Eiraku N, Machigashira K, Tagoh H, Ogata A, et al.** Elevated levels of interleukin-6 in serum and cerebrospinal fluid of HTLV-I-associated myelopathy/tropical spastic paraparesis. J Neurol Sci. 1990;97:183-93.
181. **Ohbo K, Sugamura K, Sekizawa T, Kogure K.** Interleukin-6 in cerebrospinal fluid of HTLV-I-associated myelopathy. Neurology. 1991;41:594-5.
182. **Tsukada N, Tanaka Y, Yanagisawa N.** Autoantibodies to brain endothelial cells in the sera of patients with human T-lymphotropic virus type I associated myelopathy and other demyelinating disorders. J Neurol Sci. 1989;90:33-42.
183. **Gessain A, Saal F, Gout O, Daniel MT, Flandrin G, de-Thé G, et al.** High human T-cell lymphotropic virus type 1 proviral DNA load with polyclonal integration in peripheral blood mononuclear cells of French West Indian, Guianese, and African patients with tropical spastic paraparesis. Blood. 1990;75:428-33.
184. **Matutes E, Dalgleish AG, Weiss RA, Joseph AP, Catovsky D.** Studies in healthy human T-cell-leukemia lymphoma virus (HTLV-I) carriers from the Caribbean. Int J Cancer. 1986;38:41-5.
185. **Jacobson S, Zaninovic V, Mora C, Rodgers-Johnson P, Sheramata WA, Gibbs CJ Jr, et al.** Immunological findings in neurological diseases associated with antibodies to HTLV-I: activated lymphocyts in tropical spastic paraparesis. Ann Neurol. 1988;23(Suppl. 1):S196-200.
186. **Itoyama Y, Minato S, Kira J, Goto I, Sato H, Okochi K, et al.** Altered subsets of peripheral blood lymphocytes in patients with HTLV-I associated myelopathy (HAM). Neurology. 1988;38:816-8.
187. **Mori M, Kinoshita K, Ban N, Yamada Y, Shiku H.** Activated T-lymphocytes with polyclonal gammopathy in patients with human T-lymphotropic virus type 1-associated myelopathy. Ann Neurol. 1988;24:280-2.
188. **Minato S, Itoyama Y, Fujii N, Kira J, Goto I, Yamamoto N.** Activated T cells in HTLV-I-associated myelopathy: autologous mixed lymphocyte reaction. Ann Neurol. 1989;26:398-401.
189. **Jacobson S, Gupta A, Mattson D, Mingioli E, McFarlin DE.** Immunological studies in tropical spastic paraparesis. Ann Neurol. 1990; 27:149-56.
190. **Itoyama Y, Minato S, Kira J, Goto I, Sato H, Okochi K, et al.** Spontaneous proliferation of peripheral blood lymphocytes increased in patients with HTLV-I-associated myelopathy. Neurology. 1988;38:1302-7.
191. **Kramer A, Jacobson S, Reuben JF, Murphy EL, Wiktor SZ, Cranton B, et al.** Spontaneous lymphocyte proliferation in symptomfree HTLV-1 positive Jamaicans [Letter]. Lancet. 1989;2:923-24.
192. **Tendler CL, Greenberg SJ, Blattner WA, Manns A, Murphy E, Fleisher T, et al.** Transactivation of interleukin 2 and its receptor induces immune activation in human T-cell lymphotropic virus type I-associated myelopathy: pathogenic implications and a rationale for immunotherapy. Proc Natl Acad Sci USA. 1990;87:5218-22.
193. **Yamaguchi K, Nishimura Y, Kiyokawa T, Takatsuki K.** Elevated serum levels of soluble interleukin-2 receptors in HTLV-I-associated myelopathy. J Lab Clin Med. 1989;114:407-10.
194. **Li Q, Sugimoto M, Imamura F, Matsushita F, Araki S.** Immunological abnormalities in HTLV-I associated myelopathy: spontaneous release of interleukin-2 and interleukin-2 receptor by peripheral blood lymphocytes. Jpn J Med. 1990;29:487-92.
195. **Greenberg SJ, Tendler C, Burton J, Blattner W, Waldmann T.** Alternate molecular mechanisms underlying HTLV-1 retroviral disease expression in HAM/TSP and ATL. Neurology. 1991;41: 317-21.
196. **Jacobson S, Shida H, McFarlin de, Fauci AS, Koenig S.** Circulating $CD8^+$ cytotoxic T lymphocytes specific for HTLV-I pX in patients with HTLV-I associated neurological disease. Nature. 1990;348: 245-8.
197. **Jacobson S, Reuben JS, Streilein RD, Palker TJ.** Induction of $CD4^+$, human T lymphotropic virus type-1-specific cytotoxic T lymphocytes from patients with HAM/TSP. J Immunol. 1991;146: 1155-62.
198. **Fujihara K, Itoyama Y, Yu F, Kubo C, Goto I.** Cellular immune surveillance against HTLV-I infected T lymphocytes in HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP). J Neurol Sci. 1991;105:99-107.
199. **Voskuhl RR, Eller N, McFarlin D, Jacobson S.** Cytotoxic T lymphocytes specific for HTLV-I in the CSF and peripheral blood of a patient with HAM/TSP [Abstract]. Neurology. 1991;41(Suppl. 1):S143.
200. **Ijichi S, Eiraku N, Osame M, Izumo S, Kubota R, Maruyama I, et al.** Activated T lymphocytes in cerebrospinal fluid of patients with HTLV-I-associated myelopathy (HAM/TSP). J Neuroimmunol. 1989;25:251-4.
201. **Usuku K, Sonoda S, Osame M, Yashiki S, Takahashi K, Matsumoto M, et al.** HLA haplotype-linked high immune responsiveness against HTLV-I in HTLV-I-associated myelopathy: comparison with adult T-cell leukemia/lymphoma. Ann Neurol. 1988;23(Suppl. 1):S143-50.
202. **Chavance M, Montplaisir N, Valette I, Schaffar-Deshayes L, Raffoux C.** Anti-HTLV-I antibodies and HLA phenotypes in the West Indies. Clin Exp Immunol. 1989;67:11-4.
203. **Kwok S, Kellogg D, Ehrlich G, Poiesz B, Bhagavati S, Sninsky JJ.** Characterization of a sequence of human T cell leukemia virus type 1 from a patient with chronic progressive myelopathy. J Infect Dis. 1988;158:1193-7.
204. **Bangham CR, Daenke S, Phillips RE, Cruickshank JK, Bell JI.** Enzymatic amplification of exogenous and endogenous retroviral sequences from DNA of patients with tropical spastic paraparesis. EMBO J. 1988;7:4179-84.
205. **Yoshida M, Osame M, Kawai H, Toita M, Kuwasaki N, Nishida Y, et al.** Increased replication of HTLV-I in HTLV-I associated myelopathy. Ann Neurol. 1989;26:331-5.
206. **Greenberg SJ, Jacobson S, Waldmann TA, McFarlin DE.** Molecular analysis of HTLV-I proviral integration and T cell receptor arrangement indicates that T cells in tropical spastic paraparesis are polyclonal. J Infect Dis. 1989;159:741-4.
207. **Kira J, Koyanagi Y, Yamada T, Itoyama Y, Gota I, Yamamoto N, et al.** Increased HTLV-I proviral DNA in HTLV-I-associated myelopathy: a quantitative polymerase chain reaction study. Ann Neurol. 1991;29:194-201.
208. **Richardson JH, Edwards AJ, Cruickshank JK, Rudge P, Dalgleish AG.** In vivo cellular tropism of human T-cell leukemia virus type 1. J Virol. 1990;64:5682-7.
209. **Minato S, Itoyama Y, Goto I, Yamamoto N.** Expression of HTLV-I antigen in cultured peripheral blood mononuclear cells from patients with HTLV-I associated myelopathy. J Neurol Sci. 1988;87: 233-44.
210. **Gessain A, Saal F, Giron ML, Lasneret J, Lagaye S, Gout O, et al.** Cell surface phenotype and human T lymphotropic virus type 1 antigen expression in 12 T cell lines derived from peripheral blood and cerebrospinal fluid of West Indian, Guyanese and African patients with tropical spastic paraparesis. J Gen Virol. 1990;71:333-41.
211. **Gessain A, Louie A, Gout O, Gallo RC, Franchini G.** Human T-cell leukemia-lymphoma virus type-I (HTLV-I) expression in fresh periphral blood mononuclear cells from patients with tropical spastic paraparesis/HTLV-I associated myelopathy. J Virol. 1991;65: 1628-33.
212. **Beilke MA, In DR, Gravell M, Hamiltion RS, Mora Ca, Leon-Mouzon M, et al.** In situ hybridization detection of HTLV-I RNA in peripheral blood mononuclear cells of TSP/HAM patients and their spouses. J Med Virol. 1991;33:64-71.
213. **Desgranges C, Bechet JM, Couderc LJ, Caubarrere I, Vernant JC.** Detection of HTLV-1 DNA by polymerase chain reaction in alveolar lymphocytes of patients with tropical spastic paraparesis. J Infect Dis. 1989;160:162-3.
214. **Lee JW, Fox EP, Rodgers-Johnson P, Gibbs CJ Jr, Piccardo P, DeFreitas E, et al.** T-cell lymphoma, tropical spastic paraparesis, and malignant fibrous histiocytoma in a patient with human T-cell lymphotropic virus, type 1. Ann Intern Med. 1989;110:239-41.
215. **Kawai H, Nishida Y, Takagi M, Nakamura K, Masuda K, Saito S, et al.** HTLV-I-associated myelopathy with adult T-cell leukemia. Neurology. 1989;39:1129-31.
216. **Yasui C, Fukaya T, Koizimi H, Kobayashi H, Ohkawara A.** HTLV-I-associated myelopathy in a patient with adult T-cell leukemia. J Am Acad Dermatol. 1991;24:633-7.
217. **Hirose S, Uemura Y, Fujishita M, Kitagawa T, Yamashita M, Imamura J, et al.** Isolation of HTLV-I from cerebrospinal fluid of a patient with myelopathy [Letter]. Lancet. 1986;2:397-8.

218. **Jacobson S, Raine CS, Mingioli ES, McFarlin DE.** Isolation of an HTLV-I like retrovirus from patients with tropical spastic paraparesis. Nature. 1988;331:540-3.
219. **Gessain A, Saal F, Vilette D, Lasneret J, Giron ML, Sigaux F, et al.** Establishment of an HTLV-I producing T cell line from peripheral blood lymphocytes of a patient with a tropical spastic paraparesis. CR Acad Sci. 1988;307:53-8.
220. **Gessain A, Saal F, Morosov V, Lasneret J, Villette D, Gout O, et al.** Characterisation of HTLV-I isolates and T lymphoid cell lines derived from French West Indian patients with tropical spastic paraparesis. Int J Cancer. 1989;43:327-33.
221. **McKhann G 2d, Gibbs CJ Jr, Mora C, Rodgers-Johson PE.** Isolation and characterization of HTLV-I from symptomatic family members with tropical spastic paraparesis (HTLV-I encephalomyeloneuropathy). J Infect Dis. 1989;160:371-9.
222. **Reddy EP, Mettus RV, DeFreitas E, Wroblewska Z, Cisco M, Koprowski H.** Molecular cloning of human T-cell lymphotrophic virus type I-like proviral genome from the peripheral lymphocyte DNA of a patient with chronic neurologic disorders. Proc Natl Acad Sci USA. 1988;85:3599-603.
223. **Imamura J, Tsujimoto A, Ohta Y, Hirose S, Shimotohno K, Miwa M, et al.** DNA blotting analysis of human retroviruses in cerebrospinal fluid of spastic paraparesis patients: the viruses are identical to human T-cell leukemia virus type-I (HTLV-I). Int J Cancer. 1988;42:221-4.
224. **Nakamura T, Tsujihata M, Shirabe S, Matsuo H, Veki Y, Nagataki S.** Characterization of HTLV-I in a T-cell line established from a patient with myelopathy. Arch Neurol. 1989;46:35-7.
225. **Sarin P, Rodgers-Johnson P, Sun DK, Thornton AH, Morgan OS, Gibbs WN, et al.** Comparison of a human T-cell lymphotropic virus type 1 strain from cerebrospinal fluid of a Jamaican patient with tropical spastic paraparesis with a prototype human T-cell lymphotropic virus type I. Proc Natl Acad Sci USA. 1989;86:2021-5.
226. **Tsujimoto A, Teruuchi T, Imamura J, Shimotohno K, Miyoshi I, Miwa M.** Nucleotide sequence analysis of a provirus derived from HTLV-1-associated myelopathy (HAM). Mol Biol Med. 1988;5:29-42.
227. **Daenke S, Nightingale S, Cruickshank JK, Bangham CR.** Sequence variants of human T-cell lymphotropic virus type I from patients with tropical spastic paraparesis and adult T-cell leukemia do not distinguish neurological from leukemic isolates. J Virol. 1990;64:1278-82.
228. **Evangelista A, Maroushek S, Minnigan H, Larson A, Retzel E, Haase A, et al.** Nucleotide sequence analysis of a provirus derived from an individual with tropical spastic paraparesis. Microb Pathog. 1990;8:259-78.
229. **Kinoshita T, Tsujimoto A, Shimotohno K.** Sequence variations in LTR and env regions of HTLV-I do not discriminate between the virus from patients with HTLV-I-associated myelopathy and adult T-cell leukemia. Int J Cancer. 1991;47:491-5.
230. **Gessain A, Yanagihara R, Franchini G, Garruto RM, Jenkins CL, Ajdukiewicz AB, et al.** Highly divergent molecular variants of human T-lymphotropic virus type 1 from isolated populations in Papua New Guinea and the Solomon Islands. Proc Natl Acad Sci USA. 1991;88:7694-8.
231. **Komurian F, Peloquin F, de The G.** In vivo genomic variability of human T-cell leukemia virus type I depends more upon geography than upon pathologies. J Virol. 1991;65:3770-8.
232. **Seiki M, Hattori S, Hirayama Y, Yoshida M.** Human adult T-cell leukemia virus: complete nucleotide sequence of the provirus genome integrated in leukemia cell DNA. Proc Natl Acad Sci USA. 1983;80:3618-22.
233. **Gray GS, White M, Bartman T, Mann D.** Envelope gene sequence of HTLV-I isolate MT-2 and its comparison with other HTLV-I isolates. Virology. 1990;177:391-5.
234. **Paine E, Garcia J, Philpott TC, Shaw G, Ratner L.** Limited sequence variation in human T-lymphotropic virus type 1 isolates from North American and African patients. Virology. 1991;182:111-23.
235. **Gessain A, Gallo RC, Franchini G.** Low degree of HTLV-I genetic drift in vivo as a means of monitoring viral transmission and movement of ancient human populations. J Virol. 1992;66:2288-95.
236. **Duncan J, Rudge P.** Methylprednisolone therapy in tropical spastic paraparesis [Letter]. J Neurol Neurosurg Psychiatry. 1990;53:173-4.
237. **Izumo S, Usuku K, Osame M, Arimura K, Igata A.** Effect of alpha-interferon treatment on HTLV-I associated myelopathy (HAM) [Abstract]. Neurology. 1988;39(Suppl. 1):242.
238. **Matsuo H, Nakamura T, Shibayama K, Nagasato K, Tsujihata M, Nagataki S.** Long-term follow-up of immunomodulation in treatment of HTLV-I-associated myelopathy [Letter]. Lancet. 1989;1:790.
239. **Matsuo H, Nakamura T, Tsujihatta M, Kinoshita I, Satoh A, Tomita I, et al.** Plasmapheresis in treatment of human T-lymphotropic virus type-I associated myelopathy. Lancet. 1988;2:1109-13.
240. **Nakamura T, Shibayama K, Nagasato K, Matsuo H, Tsujihata M, Nagataki S.** The efficacy of interferon-alpha treatment in human T-lymphotropic virus type-I-associated myelopathy. Jpn J Med. 1990;29:362-7.
241. **Shibayama K, Nakamura T, Nagasato K, Shirabe S, Tsujihata M, Nagataki S.** Interferon-alpha treatment in HTLV-I-associated myelopathy. Studies of clinical and immunological aspects. J Neurol Sci. 1991;106:186-92.
242. **Harrington WJ Jr, Sheremata WA, Snodgrass SR, Emerson S, Phillips S, Berger JR.** Tropical spastic paraparesis/HTLV-I-associated myelopathy (TSP/HAM): Treatment with an anabolic steroid danazol. AIDS Res Hum Retroviruses. 1991;7:1031-4.
243. **Matsushita S, Mitsuya H, Reitz MS, Broder S.** Pharmacological inhibition of in vitro infectivity of human T lymphotropic virus type I. J Clin Invest. 1987;80:394-400.
244. **Gout O, Gessain A, Iba-Zizen M, Kouzan S, Bolgert F, de Thé G, et al.** The effect of zidovudine on chronic myelopathy associated with HTLV-1 [Letter]. J Neurol. 1991;238:108-9.
245. **Sheremata WA, Squilicote DC, DeFreitas E.** A safety study of high-dose retrovirus (AZT) in HTLV-1-associated myelopathy (HAM): evidence for safety and possible efficacy [Abstract]. Neurology. 1991;41:142.
246. **Vogt WA, Lazar R, Kula RW, Harashima T, Bhagavati S, Poiesez BH.** P249. Safety and efficacy of retrovirus (zidovudine: AZT) in human T lymphotropic virus type I-related tropical spastic paraparesis: preliminary data [Abstract]. Ann Neurol. 1990;28:280.
247. **Gardner MB.** Retroviral spongiform polioencephalomyelopathy. Rev Infect Dis. 1985;7:99-110.
248. **DesGroseillers L, Rassart E, Robitaille Y, Jolicoeur P.** Retrovirus-induced spongiform encephalopathy: the 3'-end long terminal repeat-containing viral sequences influence the incidence of the disease and the specificity of the neurological syndrome. Proc Natl Acad Sci USA. 1985;82:8818-22.
249. **Paquette Y, Hanna Z, Savard P, Brousseau R, Robitaille Y, Jolicoeur P.** Retrovirus-induced murine motor neuron disease: mapping the determinant of spongiform degeneration within the envelope gene. Proc Natl Acad Sci USA. 1989;86:3896-900.
250. **Gonzalez-Dunia D, Grimber G, Briand P, Brahic M, Ozden S.** Tissue expression pattern directed in transgenic mice by the LTR of an HTLV-1 provirus isolated from a case of tropical spastic paraparesis. Virology. 1992;187:705-10.
251. **Kira J, Itoyama Y, Koyanagi Y, Tateishi J, Kishikawa M, Akizuki S, et al.** Presence of HTLV-I proviral DNA in central nervous system of patients with HTLV-I-associated myelopathy. Ann Neurol. 1991;31:39-45.
252. **Watabe K, Saida T, Kim SU.** Human and simian glial cells infected by human T-lymphotropic virus type I in culture. J Neuropathol Exp Neurol. 1989;48:610-9.
253. **Yamada M, Watabe K, Saida T, Kim SU.** Increased susceptibility of human fetal astrocytes to human T-lymphotropic virus type I in culture. J Neuropathol Exp Neurol. 1991;50:97-107.
254. **Sawada M, Suzumura A, Yoshida M, Marunouchi T.** Human T-cell leukemia virus type I trans activator induces class I major histocompatibility complex antigen expression in glial cells. J Virol. 1990;64:4002-6.
255. **Motomura M, Nakamura T, Nagasato K, Shibayama K, Kubo S, Nakasono I, et al.** HTLV-1 associated myelopathy in an identical twin [Letter]. Lancet. 1989;336:55.