NEUROLOGICAL ASPECTS OF TROPICAL DISEASE

HTLV-1 and HIV infections of the central nervous system in tropical areas

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In tropical areas, the human T lymphotropic virus type 1 (HTLV-1) infection is often superimposed on the human immunodeficiency virus (HIV) endemic. However, from a clinical point of view, the neurological consequences of HTLV-1 infection are not as prevalent as those of HIV infection. Only 0.25% of the HTLV-1 carriers develop a progressive myelopathy.[1] By contrast, CNS complications of HIV infection are frequent and often lethal. Most (89%) of the 30.6 million HIV infected people are estimated to live in sub-Saharan Africa and developing countries of Asia,[2] but the neurological complications have been well described in other populations. By contrast, HTLV-1 infection is mostly confined to tropical areas. This review highlights the differences in the neurological complications of HIV infection, and the management of these complications in tropical countries from other parts of the world, and discusses HTLV-1 infections.

HIV infection

Neurological disorders complicate HIV infection in 30% to 40% of patients, and any part of the neuraxis may be affected.[3 4] Furthermore, some studies have shown neuropathological abnormalities in 75% to 90% of patients dying with AIDS.[3 5–7] In tropical countries CNS abnormalities are also frequent in clinical and postmortem studies.[6–14] Early CNS infection is usually asymptomatic or responsible for rare disorders such as acute aseptic meningitis or encephalitis.[15 16] During the later stages of infection both the major CNS opportunistic infections and AIDS dementia complex develop.[4 17] Since 1996, the use of highly active antiretroviral therapy has decreased morbidity and mortality in HIV infected patients with advanced disease.[18 19] Incidence rates of neurological manifestations such as HIV associated neuropsychological impairment and opportunistic infections seem to have declined.[20–22] Unfortunately, in most tropical countries, antiretroviral therapy is not available and diagnostic tools are often limited. Although difficult to determine, the prevalence of neurological complications in tropical countries seems different compared with occidental countries.[7 11 17 23] Thus HIV infections in tropical countries could kill patients before the other neurological manifestations have the time to develop. In these countries, three treatable opportunistic infections— namely, cryptococcal meningitis, toxoplasmosis, and tuberculosis (table 1) cause most of the morbidity and mortality.[4–12 23–31] The different profile of neurological manifestations between tropical and industrialised countries could reflect local geographical or socioeconomic conditions and variation in risk factors.[7 11 17]

CRYPTOCOCCAL MENINGITIS (CM)

Cryptococcal meningitis is the most common life threatening fungal opportunistic infection in HIV infected patients.[32] The estimated incidence of CM in these patients varies between 5% and 10% in the United States and 30% in tropical countries such as sub-Saharan Africa, Asia, and South and Central America.[6–9 11 23 25–28 31 32] In Zimbabwe, CM accounts for 45% of all laboratory proved

Table 1 Central nervous system complications of patients infected with HIV

	Necropsy series			*Clinical series*		
Countries	*France*[5]	*India*[11]	*Brazil*[7]	*Côte d'Ivoire*[12]	*Mexico*[23]	*USA*[23]
Number of patients	148	67	230	42	40	130
Period of study	1982–1988	1988–1996	1985–1990	1995	1986–1988	1986–1988
Focal disorders						
Cerebral toxoplasmosis	44%	16%	34%	36%	7.5%	4.6%
Primary lymphoma	11%	0	4%	0	2.5%	8.4%
Progressive multifocal leucoencephalopathy	3%	0	0	0	2.5%	3.8%
Non-focal diseases						
Cytomegalovirus encephalitis	17%	9%	7.9%	0	0	18.5%
Meningitis						
Cryptococcal meningitis	1%	10%	13.5%	12%	17.5%	13%
Tuberculosis	0.6%	15%	0	7%	10%	1%
Aseptic meningitis	NA	NA	NA	0%	7.5%	6.1%
Bacterial meningitidis	NA	NA	NA	12%%	0	0

NA=not available.

cases of meningitis in adults.[24] The high rate of cryptococcal infection in tropical countries seems to be due to the usual presence of *Cryptococcus neoformans* in the environment of patients with AIDS.[33] Although unusual (25% to 30% of patients), meningeal symptoms may be seen with CM.[32] If available, the latex agglutination test for cryptococcal antigen detection in both serum and CSF is a highly sensitive and specific procedure in the diagnosis of cryptococcosis and can be used as a screening tool in febrile patients.[32] Despite treatment, mortality in the acute stage of CM remains high (10%-25%) and the 1 year survival rate is about 30%-60%.[33–35] In Malawi, the median survival was 4 days without treatment after CM had been diagnosed.[28] In a prospective study from Zimbabwe focusing on natural history of CM, the cumulative median survival was 14 days (0 to 233 days) and the 1 month survival rate was 22%.[24] Thus, many patients seem to have an indolent course even without treatment. The treatment consists of intravenous amphotericin B (0.7 mg/kg/day).[33] Cost, need for parenteral administration, and toxicity are the main limitations of use of amphotericin B. Fluconazole has shown similar rates of treatment success to those of low doses (0.4 mg/kg/day) of intravenous amphotericin B.[34] However, in America the 2 week mortality was higher in the fluconazole group than in the amphotericin B group (15% *v* 8%). The current recommendation for treatment of CM is to use amphotericin B (0.7 mg/kg/day) and flucytosine (25 mg/kg four times daily).[36] After 2 weeks, this combination may be supplanted by oral fluconazole (400 mg/day) for 8 weeks (table 2). This therapy seems very successful (6% of initial mortality and 8% of overall mortality).[36] Lifelong maintenance therapy is essential to prevent relapse of CM.[32] Fluconazole (200 mg daily) has now been shown to be more effective and better tolerated than amphotericin B and is the preferred agent for secondary prophylaxis.[37] Unfortunately, in many tropical countries, this antifungal treatment is not available. These antifungal agents were not included in the list of essential drugs needed in Zimbabwe.[24] Cost of the induction phase of therapy for CM amounts to several times the average monthly salary in Zimbabwe and in many resource poor sub-Saharan African countries.[24 28] Easily managed and cost effective treatments are absolutely necessary for CM in developing countries. A comparative 2 month study of fluconazole (200 mg/day) with flucytosine (150 mg/kg/day) for the first 2 weeks with fluconazole alone at the same dose in 58 Ugandan patients showed a lower initial mortality in the combination group (16% *v* 40%).[29] After 4 months of maintenance therapy (fluconazole at 200 mg three times weekly), survival rate was higher in the combination group (32% *v* 12%).

TOXOPLASMOSIS ENCEPHALITIS (TE)

Toxoplasmosis encephalitis is the most common opportunistic infection causing encephalitis or focal cerebral lesions.[38] About 3% to 40% of patients with AIDS will develop TE (table 1).[38 39] In tropical countries, the frequency of TE in necropsy series of AIDS patients is high: 34% in Brazil,[7] 23% in Côte d'Ivoire,[30]and 19% in India.[11] Risks factors for TE are a previous *Toxoplasma gondii* infection and a CD4+ cell count< 100/mm^3.[40] Geographical differences in TE rates among patients with AIDS may be explained by the worldwide observed variation of *Toxoplasma* IgG seroprevalence.[40] TE presents with a constellation of symptoms and signs, of which only chorea is thought to be pathognomonic in patients with AIDS.[38] Diagnosis is made on the basis of clinical symptoms and CT or MRI findings (contrast enhancing space occupying lesions of the brain).[38] In tropical countries where CT is not available, the diagnosis should be made on clinical grounds and fast response to presumptive therapy.

The current recommended therapy of TE is a 4 to 8 week course of sulfadiazine and pyrimethamine.[38 41] Adverse reactions to these medications are common, occurring in as many as 25% to 53% of patients.[38 41] Alternative less toxic medications—namely, azithromycin, clarithromycin, atovaquone, and trimethoprim-sulfamethoxazole (TMP-SMZ)—are under investigation.[42–44] In an open study, we have followed up 21 patients who were treated with TMP-SMZ (160 mg trimethoprim and 800 mg sulfamethoxazole three times daily by oral or

Table 2 Treatment and prophylaxis of cryptoccocosis and toxoplasmosis in HIV infection

	First choice	*Alternative*
Cryptoccocosis		
Acute infection	Amphotericine B, 0.7 mg/(kg.day) iv and flucytosine, 100 mg/(kg.day) orally or iv in 4 divided doses for 2 weeks, then fluconazole, 400 mg orally four times daily for 8 weeks	Fluconazole, 400 mg orally four times daily for 10 weeks, or Fluconazole 200–400 mg orally four times daily for 10 weeks and flucytosine 150 mg/(kg.day) orally or iv in 4 divided doses for 2 weeks
Suppressive therapy	Fluconazole 200 mg orally four times daily	Amphotericine B, 0.6–1.0 mg/kg iv four times weekly, or Itraconazole, 200 mg orally four times daily
Toxoplasmosis		
Acute infection	Pyrimethamine 100–200 mg loading dose (2 days), then 50–100 mg orally four times daily plus folinic acid 10 mg orally four times daily+ sulfadiazine 4–8 g orally four times daily for at least 6 weeks	Pyrimethamine plus acid folinic plus clindamycin 900–1200 mg iv four times/6h or 300–450 mg orally four times/6h for at least 6 weeks, or Trimethoprim, 160 mg plus sulfamethoxazole, 800 mg/8h orally or iv for at least 6 weeks
Suppressive therapy	Pyrimethamine 25–75 mg orally four times daily plus folinic acid 10 mg orally four times daily + sulfadiazine 500–1000 mg orally four times/6 h	Pyrimethamine plus acid folinic plus clindamycin 300–450 mg orally four times/6h, or Trimethoprim, 160 mg plus sulfamethoxazole, 800 mg orally four times daily
Prophylaxis (patients with positive IgG serology and CD4 count <100/mm^3)	Trimethoprim, 160 mg plus sulfamethoxazole, 800 mg orally four times daily	Dapsone 50 mg/day plus pyrimethamine 50 mg/week plus folinic acid 25 mg/week

intravenous route for 4 to 6 weeks).[44] Clinical and radiological improvements were achieved in 94% of patients. Severe toxicity leading to alternative treatment occurred in two patients. Considering large availibility, good tolerance, easy management, and low cost, TMP-SMZ seems a treatment of choice for TE in tropical countries.[31]

TUBERCULOSIS (TB)

One third of the world's population is thought to be infected with *Mycobacterium tuberculosis.*[45] In 1990, the WHO estimated that active disease occurs in 8 to 10 million people and that 3 million people died of TB each year.[45] HIV infection is the strongest risk factor for the progression of latent *M tuberculosis* infection to active TB.[46] By mid-1995, nearly 7 million people worldwide were estimated to be coinfected with *M tuberculosis* and HIV, of whom 4 million live in Africa, 3 million in south and south east Asia, and 0.4 million in Latin America and the Caribbean basin.[47 48] TB is a major cause of death in patients infected with HIV worldwide. In Abidjan (Côte d'Ivoire) TB was seen in 54% of AIDS cadavers.[30] In sub-Saharan African countries, in which the rates of HIV infection are the highest, the incidence of TB has more than doubled since the early 1980s.[47 48] In Asia, the expanded HIV epidemic has led to occurrence of new cases of TB attributable to HIV, with the same magnitude as in sub-Saharan Africa.[47] In North American or European studies, CNS TB is unusual and occurs in 5% to 10% of patients infected with HIV.[48–50] HIV infection does not seem to alter the clinical and laboratory manifestations or the prognosis of TB meningitis. By contrast with non-HIV infected patients, CNS mass lesions, including cerebral abscesses and tuberculomas, are more often demonstrated by CT or MRI in patients with AIDS.[51] In tropical countries, TB meningitis is a relatively frequent complication of HIV infection, and such infection is often undiagnosed (table 1). Despite antituberculous drugs, the mortality of TB meningitis remains high.[51] In resource poor tropical countries, antituberculous regimens containing rifampin are often unavailable.

AIDS-DEMENTIA COMPLEX (ADC)

AIDS-dementia complex is an HIV specific syndrome of subcortical dementia characterised by slowness and imprecision of cognition and motor control.[4] The earliest symptoms of ADC are cognitive and patients complain of difficulties in concentration and forgetfulness; and relatives notice difficulties in thinking. Later, diffuse motor abnormalities include ataxia, hyperreflexia, and the appearance of frontal lobe release reflexes such a snout response, are present with possible progression to tetraparesis. ADC is often associated with a vacuolar myelopathy (ataxia, spastic paraparesia, hyperreflexia, and incontinence).

ADC develops mainly in patients with severe immunosuppression. In the United States the incidence rate of ADC over a 5 year period is 7.3 cases per 100 person-years for people with CD4 counts of 100 or less.[4] In Kinshasa, the estimated prevalence of ADC was 8.7% in a cross sectional study of HIV infected patients admitted to hospital.[6] Antiretroviral therapy can only improve ADC symptoms.[4]

NEUROMUSCULAR DISORDERS

Neuromuscular disorders are common and important causes of morbidity.[4] Autoimmune demyelinating neuropathies or inflammatory myopathy usually develops in the early stage of HIV infection. The prognosis is good with corticosteroid therapy. By contrast, during the late stage of HIV infection, CMV polyradiculopathy, CMV mononeuritis multiplex, or HIV polyneuropathy distal, axonal and predominantly sensory are associated with a poor prognosis. There are few data on the frequency of these manifestation in tropical countries.

HIV INFECTION IN CHILDREN

HIV infection of children is rapidly increasing, with more than 1600 children becoming infected each day. Most of these infections occur in sub-Saharan Africa, where over 22 million children are infected with HIV. Most children acquire HIV from their mothers, particularly during labour, but also during pregnancy, and the postnatal period from breast milk. Blood transfusion for the treatment of severe anaemia and malaria is another important source in developing countries.[52]

HIV readily infects the developing CNS of children, and is a major cause of morbidity and contributes to the fatal outcome.[53] Postmortem studies show that most children dying with AIDS have evidence of neurological involvement.[54] Children more often have a HIV encephalitis, and less superimposed infections and lymphoma than adults,[55] particularly children living in tropical countries.[56]

HIV infection of the CNS usually manifests after other clinical features of HIV infection. The most common manifestations in Europe and North America are delayed development, loss of developmental milestones, cerebral atrophy, and pyramidal tract signs. The progressive encephalopathy (with loss of milestones and cerebral atrophy) usually occurs before the age of 3 years, and is associated with a high viral load and early decrease in CD4 lymphocytes.[57] Other neurological manifestations include stroke,[58] extrapyramidal,[59] and cerebellar signs, and peripheral neuropathies.[60]

In Africa, perinatal HIV infection is associated with motor and cognitive delay.[61] In birth cohort studies from Rwanda and Uganda, abnormal neurological signs were elicited in 15%-40% of HIV infected children during the first 2 years of life.[62] Most of these children have developmental delay, with a reduction in the growth of the head circumference, suggesting cerebral atrophy. Studies from Rwanda suggest that progressive encephalopathy is relatively rare.[63]

HTLV-1 infection

In 1964, a progressive thoracic myelopathy was described in Jamaican adults and this disorder was termed tropical spastic paraparesis

Table 3 Symptoms and signs of HAM/TSP

	Vernant et al[68] *n=25*	*Araujo et al*[73] *n=34*	*Bhigjee et al*[74] *n=24*
Race	Afro-Caribbean	Mainly white	Bantu
Mean duration	8 years	7 years	Less than 1 year
Symptoms (%):			
Leg weakness	100	97	100
Backache	28	44	49
Painful legs	40	Occasional	Unknown
Paraesthesias	44	21	45
Urinary frequency or incontinence	96	94	78
Signs (%):			
Leg spasticity	100	88	100
Arm spasticity	92	18	82
Inability to walk	44	9	50
Ability to walk	56	91	50
Sensory level	4	14	49
Abnormal superficial sens.	40	27	53
Abnormal deep sensitivity	28	62	49

(TSP).[64] In 1985, Gessain *et al* clarified the aetiology of TSP by reporting in Martinique that 60% of these patients had antibodies to HTLV-1.[65] In 1986, a similar myelopathy associated with HTLV-1 antibodies in the serum and CSF of Japanese patients was named HAM (HTLV-1-associated myelopathy) by Osame *et al.*[66] These were the same disease, ultimately labelled HAM/TSP.

CAUSATIVE ORGANISM

HTLV-1 is a type C retrovirus sharing some distinctive features with the bovine leukaemia virus (BLV) and the simian T cell leukaemia virus (STLV).[67] It has two regulatory genes: the *tax* gene which is responsible for the activation of viral replication, and the *rex* gene which, conversly, inhibits replication. Molecular analysis of HTLV-1 strains from the known endemic areas have identified three different genotypes—namely, widespread cosmopolitan subtype (HTLV-1 subtype A), large central African genotype (HTLV-1 subtype B), and Melanesian subtype (HTLV-1 subtype C).

EPIDEMIOLOGY

In tropical areas, HTLV-1 infection is endemic near the equator. Caribbean basin,[68] Colombia, and equatorial Africa[69] were the first high frequency pockets to have been reported. Numerous epidemiological studies have shown that HTLV-1 is mainly transmitted from husband to wife and mother to child and that the risk for seroconversion of household contacts is low. Exposure to contaminated blood products is the third known source. HTLV-1 is, however, a mildly infective virus; the prevalence among insular groups (island of Tsushima) or Amerindian populations[70] illustrate the importance of geographical or cultural isolation which seems to be required for its propagation. The average age of onset of HAM/TSP is about 40 years, but it may begin between the ages of 20 and 70 years, although rarely younger than 15. Women are affected more often than men by about 1.5:1. Highest prevalence rates (100/100 000) are found in Tumaco and the Seychelles. Although some clusters have been reported in Zaire (prevalence 50/100 000), epidemiological data on the situation of HAM/TSP in Africa remain scarce. Factors determining the onset of HAM/TSP in some infected people are not yet clearly understood. Lack of correlation between seroprevalence rates and occurrence of HAM/TSP in different ethnic groups of the same country suggest that besides HTLV-1 infection, critical environmental or genetic cofactors are responsible for the disease. HAM/TSP was initially thought to affect only poor black people living in tropical countries.[71] However, its predominance among white people in Brazil demonstrates that HAM/TSP develops regardless of race and socioeconomic status. A recent Jamaican case-control study showed that an early age of initial sexual intercourse and more than five lifetime sexual partners increase the risk of HAM/TSP.[72] Finally, patients have developed seroconversion and HAM/TSP in as little as 6 months after transfusion with contaminated blood products.

CLINICAL FEATURES

The most common initial symptom in patients with HAM/TSP is either leg weakness or difficulty in walking (table 3).[68 73 74] Other common symptoms are painful legs, paraesthesias, back pain, and bladder dysfunction. The most common neurological sign is a spastic paraparesis which is asymmetric in one third of patients. Frequency of loss of touch and pain sensation ranges from 27% to 53% of the patients in three major series.[68 73 74] HAM/TSP usually presents with an insidious course. However, the evolution of the disease is rapid and aggressive in South Africa[74] and spontaneous improvement has been reported among patients with definite HAM/TSP.[75] Whatever the course of HAM/TSP, the clinical impression is that the neurological disability becomes relatively stable a few years after onset.[76] Some authors have noted a down beat nystagmus suggesting that the lesions in HAM/TSP are not limited to the spinal cord but extend to the brainstem. Optic neuropathy (15%) was described among the original patients with HAM/TSP.[64] There are, however, a few cases of somewhat atypical HAM/TSP during the course of which optic neuritis occurs, thereby suggesting the diagnosis of multiple sclerosis with fortuitous HTLV-1 infection. On the other hand, convincing epidemiological data have shown a positive association between HTLV-1 and facial nerve palsy[77] and chronic hypertrophic pachymeningitis, which may eventually explain multiple cranial nerve involvement seen in some HTLV-1 infected people. Polyneuropathy has been mentioned in the literature, but many reports lack complete clinical and neurophysiological information and it still remains premature to conclude that HTLV-1 is a causal agent in polyneuropathy. Polymyositis or anterior cell degeneration linked to HTLV-1 sometimes develop in the presence[78] or in the absence of HAM/TSP. Finally, the coexistence of systemic symptoms including alveolitis,[79] sicca syndrome,[79 80] arthritis, and infective dermatitis are the striking features of HAM/TSP.

LABORATORY FEATURES

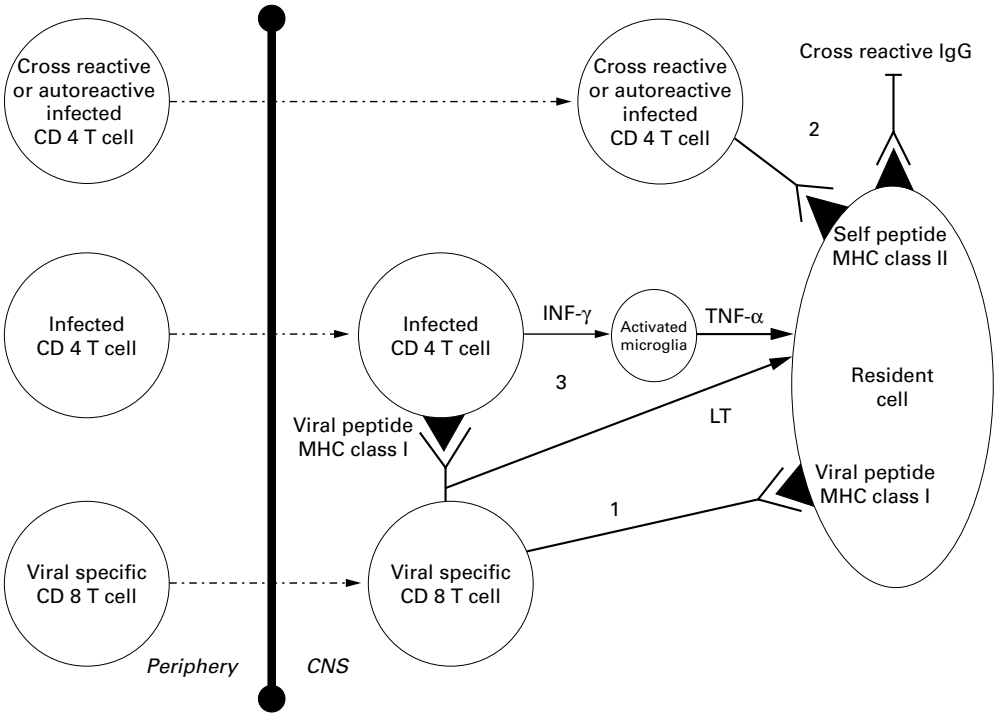
A common feature is the presence of atypical lymphocytes with convoluted nuclei (flower cells) in the blood of infected patients.[81] Higher

titre specific anti-HTLV-1 antibody is present in the serum of patients with HAM/TSP than in asymptomatic carriers. The CSF demonstrates an intrathecal IgG synthesis (sensitivity 95%) and a high local synthesis of HTLV-1 antibodies (sensitivity 85%) in patients with HAM/TSP.[82] Most patients with HAM/TSP also show an intrathecal immune response against HTLV-1 synthetic peptides (especially against HTLV-1 env gp21 synthetic peptides)[83] contrasting with a poor polyspecific one against common viruses as seen in multiple sclerosis. Lower limb somatosensory evoked potential (SEP) studies detect unilateral or bilateral sensory spinal cord lesions in many patients with HAM/TSP.[84] The most useful neurophysiological parameter seems to be the central sensory conduction time, which correlates well with disability score.[84] Experience with brainstem auditory evoked potentials supports a supraspinal involvment in some HAM/TSP patients. Motor pathway analysis is consistent with pathology affecting mainly the thoracolumbar cord. Magnetic resonance imaging of the spinal cord shows some degree of atrophy at the level of lower thoracic cord. Brain MRI usually shows white matter lesions similar to those seen in multiple sclerosis.[85] Frequency of small deep and subcortical white matter, small infratentorial and large periventricular lesions is lower in HAM/TSP than in multiple sclerosis.

PATHOGENESIS OF HAM/TSP

Lesions in HAM/TSP invariably predominate in the pyramidal tracts of the middle and lower thoracic spinal cord. They consist of a severe demyelination, perivascular, and parenchymal mononuclear infiltrates (T and B lymphocytes and macrophages), reactive astrocytosis, microglial proliferation, and loss of axons.[86] CD4+T cells and CD8+T cells are present equally in the early stage of the disease whereas CD8+T cells predominate in the late stage.[86] In situ polymerase chain reaction of HTLV-1 proviral DNA has shown CD4+T cells to be the likely preferential virus reservoir in the CNS.[87] Others found HTLV-1 DNA in areas devoid of immune cell infiltration.[88] Expression of major histocompatibility complex (MHC) class I and class II molecules is increased on both T cells and glial cells. Interferon (IFN)-γ,[89] interleukin (IL)-6, IL-1, granolocyte-macrophage colony stimulating factor, tumour necrosis factor (TNF)-α negative, and TNF-α positive cells have been detected in the CSF of HAM/TSP patients. Cytokine expression in some spinal cord lesions is gradually down regulated and together with the duration of illness is correlated with the decrease of CD4+/CD8+T cell ratio.[90]

The promoter of the disease remains, however, unclear. There are at least three mechanisms through which, either alone or in combination, HTLV-1 infection could result in spinal cord injury in very few (0.25%) infected people (figure). The cytotoxic hypothesis proposes that resident cells infected by CD4+T cells could process viral proteins in immunogen peptides resulting in a specific attack by cytotoxic lymphocytes (CTL) and subsequent CNS damage.[91] Supporting the cytotoxic hypothesis, Lehky *et al* found by in situ hybridisation HTLV-1 *tax* m-RNA in very few astrocytes, but not in infiltrating CD4 T cells in the spinal cord of patients with HAM/TSP.[92] These results have been discussed by others.[93] The autoimmune hypothesis predicts an attack of CNS cells by either reactive T cells cross reacting with a CNS



Pathogenesis of HAM/TSP. 1=cytotoxic hypothesis; 2=autoimmune hypothesis; 3=bystander damage hypothesis; LT=lymphotoxin.

antigen or CNS autoreactive CD4+T cells. Interestingly, the requirement of costimulatory molecules of the B7 family for autoreactivity is negated by HTLV-1 infection.[94] The exact proportion of self reactive T cells in the spinal cord lesions and the idenfication of the autoantigens involved in the autoimmune hypothesis require, however, further investigation. The bystander damage hypothesis speculates an immune reaction within the CNS without immune specificity for the CNS cells. Productively infected CD4+T cells would be the targets of the virally reactive CD8+T cells.[95] Lesions of the CNS could result from myelinotoxic cytokines including TNF-α and lymphotoxin, respectively secreted by activated microglia and CD8+ T cells. The bystander damage hypothesis requires the presence of infected CD4+ T cells in the spinal cord, but this point remains a matter of controversy.

Recently, damage to the blood-brain barrier has been thought to be involved in the pathogenesis of HAM/TSP. Some findings suggest that VLA-4/VCAM-1 interaction may play a major role in mediating lymphocyte migration into the CNS. Matrix degrading metalloproteinases are a constant finding in CSF of patients with HAM/TSP.[96] The host and viral factors that determine which infected people develop HAM/TSP are as yet poorly understood. There is to date no convincing data supporting specific HAM/TSP related mutations within the genome of the virus. By contrast, HLA haplotypes correlated with development of HAM/TSP in Japan and were associated with a high immune and intrathecal responsiveness against the virus. In addition, only the WKAH rat model of HAM/TSP emphasised the possible role of genetic host factors.

TREATMENT OF HAM/TSP

Based on the inflammatory nature of the CNS lesions in HAM/TSP, immunomodulatory agents were assessed in this disease. Some patients with HAM/TSP from Japan seemed to have a good response to steroid therapy,[97] but the initial benefit disappeared with long term follow up, and has not been found in tropical areas. Clinical improvement under immunosuppressive agents such as azathioprine or cyclophosphamide was only marginal.[98] Blood purification[98] or high doses of intravenous immunoglobulins provided no sustained clinical benefits. The dramatic efficacy of high dose vitamin C in a small open trial[99] was not later confirmed. Five out of seven patients treated by IFN-α during the 22 week period of treatment, showed an improvement in motor performance which lasted up to 6 months. However, in another series of 43 patients, only 10 (23.3%) improved by more than one grade in motor disability scale.[98] Finally, antiretroviral drugs such as zidovidine were ineffective.

The presumed role in the pathogenesis of HAM/TSP of proinflammatory soluble mediators suggests new treatments. Inhibitors of TNF-α production may be beneficial.[100] Also, therapeutic trials assessing inhibitor agents of MMPs or molecules involved in cell to cell adhesion could be conducted. However, considering the gradual decline of inflammatory lesions in the spinal cord of the affected patients, these potential agents must be assessed on a selected population in the early stage of HAM/TSP. In the late stage, only symptomatic therapies as physiotherapy or possibly intrathecal baclofen deserve consideration.

Conclusion

Although a definitive therapy is lacking for HAM/TSP, this disorder does not represent a major problem in tropical countries. In addition, a gradual decline in HTLV-1 seroprevalence and subsequent incidence of HAM/TSP can be expected in future, at least in some countries such as the French West Indies, with effective prevention. By contrast, HIV endemic is spreading in most of the developing countries, and neurological complications still remain a major world health problem. Inavailability of modern methods of diagnosis and treatment in HIV infected patients makes management of CNS manifestations in these areas a difficult challenge.

Illustrative case

A 52 year old black woman from Martinique West Indies presented with a 7 year history of slowly progressive weakness and stiffness in her legs as well as bladder dysfunction. Neurological examination showed a spastic paraparesis and extensor plantar responses. Western blot analysis identified antibodies to HTLV-1 in both serum and CSF. In the next year, January 1992, the patient noticed ocular and oral dryness. Although anti-SS-A and anti-SS-B antibodies were absent in serum, a positive Shirmer test and features of a biopsy specimen of the lip (Grade 4 Chisolm-Mason) were indicative of Sjögren's syndrome. In November 1992, she experienced proximal myalgia in the lower limbs, progressive dyspnoea, and blurring of vision. A biopsy specimen of the muscle was consistent with myositis. Dyspnoea at that time was related to a severe lymphocytic alveolitis, and the slit lamp study showed a bilateral anterior uveitis. Successive trials of prednisone (40 mg daily during 9 months) and cyclophosphamide (500 mg intravenously monthly during 6 months) resulted in a transient improvement of myositis, alveolitis, and uveitis. In February 1995, the patient was cachectic and paraparetic with evidence of both myelopathy and myositis. She had more difficulties in breathing and radiography of the chest evidenced a marked pulmonary fibrosis. She finally died from respiratory failure in March 1995.

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