HUMAN IMMUNODEFICIENCY VIRUS AND THE NERVOUS SYSTEM: AN UPDATE WITH EMPHASIS ON DEVELOPING COUNTRIES

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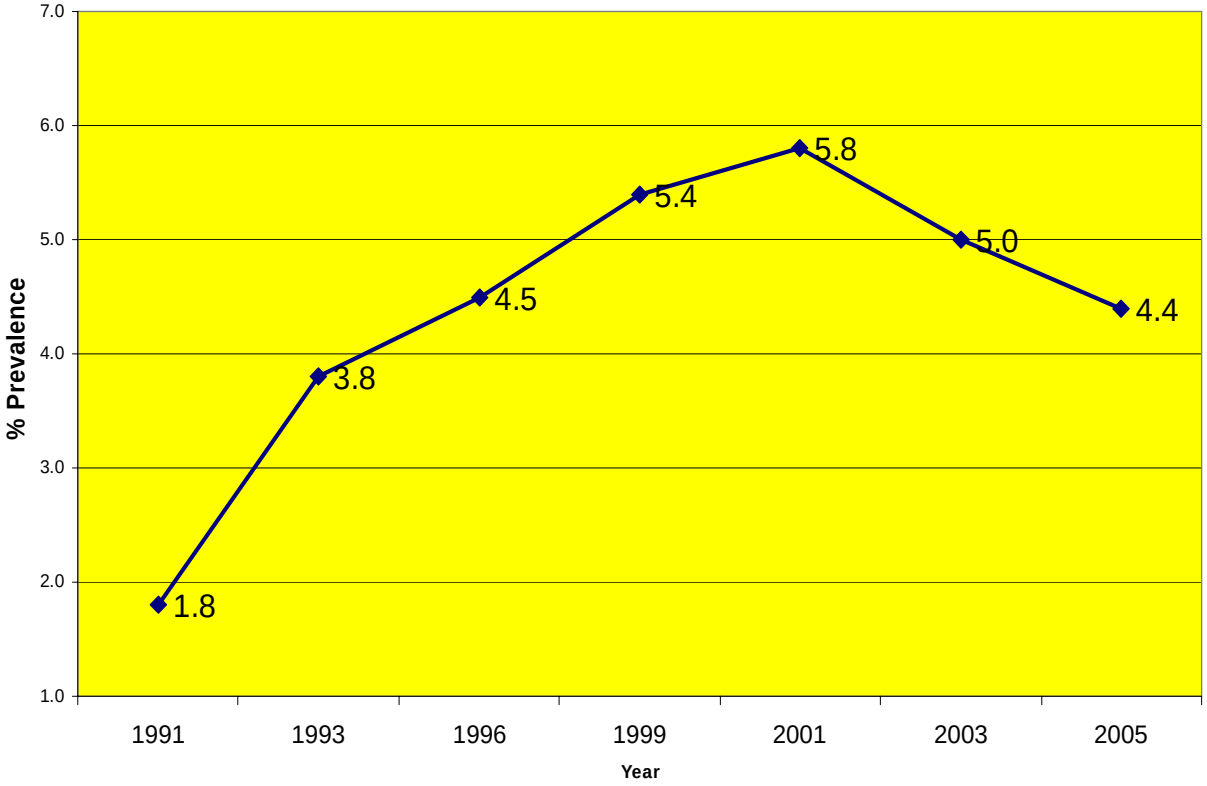
SUMMARY
Ten percent of patients that are diagnosed with AIDS also have some neurological complaint, 40% present neurological signs or symptoms during the course of the infection, and 80% of the autopsies present neurological alterations. Although much is known about the neuropathology of HIV infection, many important questions on its neuropathogenesis remain unanswered.

INTRODUCTION
The pandemic of HIV/AIDS continues to grow daily since its recognition in 1981. Human immunodeficiency virus (HIV) is a retrolentivirus causing immunosuppression, which progresses to the acquired immunodeficiency syndrome (AIDS) and eventual death. The origin of HIV in humans lies in its evolution from the simian immunodeficiency virus infection in nonhuman primates and subsequent transmission to humans in central Africa, likely through the bushmeat industry[1]. This is a speculation which has not been conclusively proven. Worldwide there are about 18,000 newly-infected people per day, with approximately 40 million infected worldwide[2]. In the United States, nearly one million people are infected with HIV[3]. Incident cases among women, intravenous drug users and ethnic minorities comprise the fastest growing segment of the HIV-infected population, and the number of HIV-infected individuals over the age of 50 is growing rapidly[1,3].

HIV infection has ravaged sub-Saharan Africa exerting profound health, social, economic and political effects that will last for generations. There are 25.8million cases in sub-Saharan Africa with 3.2 million new cases and 2.4 million deaths in 2005[2]. Nigeria is home to more people living with HIV than any other country in the world, except South Africa and India—between 3.2 and 3.6 million people at the end of 2003[2]. Median HIV prevalence among pregnant women appears to have leveled at around 4%. Although HIV prevalence among pregnant women varies (from a low of 2.3% in the South West to a high

of 7% in the North Central parts), stable trends are evident at almost all the antenatal clinics surveyed since the mid-1980s. The only exception is Cross River State, where infection levels rose from 4% in 1993-1994 to 12% in 2003[2,4].

HIV Prevalence in Nigeria (1991–2005)



Pathogenesis

HIV-1 is neurotropic (infects the nervous system) and is neurovirulent (causes disease in the nervous system)[5]. The nervous system is infected immediately after primary HIV infection with rapidly ensuing subclinical neurological injury. In fact, the severity and frequency of HIV-induced neurological disorders are influenced by host neurosusceptibility, which are determined by factors including host age, genetic polymorphisms, level of immunosuppression and concurrent infections, together with the ability of the host to contain infection at the time of primary infection[6]. During the course of infection, HIV replicates, actively producing around 10 virions that are genetically different and are related to immunological escape, higher pathogenicity, drug resistance and predisposition to infect the CNS[7,8].

The HIV penetrates the CNS during the initial phase of the infection. During this period, the viral load in the peripheral blood is as high as it is in the terminal phase of the illness[9,10]. Some researchers have identified HIV proteins[9] or intrathecal synthesis of anti-

HIV antibodies, in the initial phase of infection[11]. About 5 to 10% of patients present with acute viral meningitis, at the time that the virus is acquired or during the seroconversion phase. This acute meningitis does not differ from the point of view of the cytological or biochemical characteristics of the cerebral-spinal fluid (CSF), nor does it differ clinically from acute meningitis acquired through other viruses, such as enteroviruses. Some patients, however, do have peripheral facial palsy associated with the meningitis[3]. As the seroconversion proceeds in this phase of acute meningitis, the search for anti-HIV antibodies in serum or CSF is negative[12,13]. The penetration of HIV into the CNS through neurons by axonal flow, as occurs with herpes virus and rabies virus, is less probable because the CD4 receptor, the main receptor that enables HIV to infect the cell, is absent on neurons. A more likely possibility is penetration through a hematogenic pathway. This occurs through free particles in the CNS crossing the microvessels that compose the blood brain barrier (BBB) or the blood CSF barrier (BCB), or through infected cells, such as lymphocytes or monocytes. Possibly all of these forms of penetration are involved, acquiring greater or lesser importance depending on the phase of the infection[13]. The penetration through infected monocytes or macrophages, the "Trojan Horse" theory, is currently considered to be the main form of HIV entrance into the CNS[14,15].

The disrupted BBB during HIV infection allows free particles and infected monocytes to penetrate into the CNS. These cells can enter through tight junctions or through the endothelial cells of the capillaries, with the latter being more likely than the former. In addition to this, higher levels of matrix metalloproteinases (MMPs) in the CNS have been found. MMPs can weaken the basal membrane, facilitating the migration of leukocytes across the BBB[16]. HIV-1 infected monocytes show an increase in adhesion in endothelial and astrocyte cell cultures. Endothelial cells with modified function can increase endothelial adhesion and the infiltration of the infected monocytes in the CNS, due to alterations of the composition of proteins of the basal membrane[17]. These alterations are at the same time due to production of derivatives of the virus proper or of free chemokines, by either infected cells, non-infected cells or by the infection of astrocytes. It has been shown that HIV Tat protein activates endothelial cells, resulting in an increase of the expression of adhesion molecules, MMPs and cytokines. This results in the CNS serving as an important reservoir of HIV infection[16,18,19,20].

Neurologic manifestations

Neurological disorders complicate HIV infection in 30% to 40% of patients, and any part of the neuraxis may be affected[21,22]. Furthermore, some studies have shown neuropathological abnormalities in 75% to 90% of patients dying with AIDS[22-24]. In tropical countries CNS abnormalities are also frequent in clinical and postmortem studies[24-27]. Early CNS infection is usually asymptomatic or responsible for rare disorders such as acute aseptic meningitis or encephalitis[28]. During the later stages of infection both the major CNS opportunistic infections and AIDS dementia complex develop[21,29]. Since 1996, the use of highly active

antiretroviral therapy has decreased morbidity and mortality in HIV infected patients with advanced disease[30]. Incidence rates of neurological manifestations such as HIV associated neuropsychological impairment and opportunistic infections seem to have declined[31,32]. 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 western countries[23,25]. 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 cause most of the morbidity and mortality[21,23-26,33-34]. The different profile of neurological manifestations between tropical and industrialised countries could reflect local geographical or socioeconomic conditions and variation in risk factors.

Today, the central nervous system and the immune system are seen as main targets of HIV infection. Significant progress in the knowledge and treatment of AIDS has been obtained in recent years. The neurological manifestations directly related to HIV are acute viral meningitis, chronic meningitis, HIV-associated dementia (HAD), vacuolar myelopathy, and involvement of the peripheral nervous system.

HIV-associated dementia

The primary central nervous system manifestations of HIV, directly caused by the virus, include HIV-associated dementia (HAD), which affects 20% of untreated and 5-10% of antiretroviral-treated HIV/AIDS patients and the less severe and antecedent condition, HIV-induced Minor Cognitive-Motor Deficit, which affects another 25-30% of HIV-infected patients, regardless of combination antiretroviral therapy (ART) implementation. These disorders are defined by cognitive, behavioral and motor deficits, similar to other 'subcortical' syndromes and are associated with diminished quality of life and increased health care costs.

The remaining approximately 50% of patients exhibit no deficits of cognitive or brain function but HIV-induced peripheral nervous system disorders, particularly a distal sensory polyneuropathy, have become major clinical issues in recent years, affecting over 35% of infected patients. These neurological disorders occur in HIV-infected patients globally with similar frequencies in different geographic sites, seemingly irrespective of the HIV-1 clade (subtype) (1). With the increasing availability of ART, the incidence and severity of HAD has declined while the prevalence of both HAD and HIV associated sensory neuropathy is increasing because persons with HIV/AIDS are living longer[35-37]. Nonetheless, the development of HIV-induced CNS disease heralds a worsened survival prognosis with or without concurrent ART[38,39]. In the era of combination ART, the onset of HAD is occurring at earlier stages of the HIV/AIDS disease course with progressively higher levels of immune competence (CD4+ T cell levels 200-400 cells/µl) at the time of diagnosis. Neuronal death and injury including synapto-dendritic 'pruning' are the prototypic consequences of chronic inflammation induced by HIV-1 within

the brain and are among the neuropathological hallmarks of HAD[40].

Previously, the HAD was described as AIDS-dementia complex (ADC). This is an HIV specific syndrome of subcortical dementia characterized by slowness and imprecision of cognition and motor control[21]. 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 (which is characterized by ataxia, spastic paraparesia, hyperreflexia, and incontinence). Diagnosis of vacuolar myelopathy requires magnetic resonance imaging of the spinal cord.

ADC develops mainly in patients with severe immunosuppression. The deterioration in cognitive performances with severe immunosuppression has been demonstrated in Nigeria HIV/AIDS patients[41-43] but a study demonstrated the absence of this pattern among asymptomatic HIV seropositive patients[44]. 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[21]. In Kinshasa, the estimated prevalence of ADC was 8.7% in a cross sectional study of HIV infected patients admitted to hospital[24]. Antiretroviral therapy can only improve ADC symptoms[25].

Primary CNS lymphoma

Primary CNS lymphoma (PCNSL) is a Non-hodgkin's type of lymphoma that invades the brain, the vitreous body and nerves of the eye, the meninges, and the nerve roots of brain and spine. The mechanism of involvement of these locations by malignant B lymphocytes is unknown, but it might involve molecular targeting of lymphoma cells generated at cryptic systemic sites. Patients with HIV/AIDS are highly predisposed to develop PCNSL and it represents the most frequent brain tumor in this patient population[45]. Epstein-Barr virus (EBV) infection increases the risk of brain involvement in PCNSL[46]. The introduction in 1995 of highly active anti-retroviral therapy (HAART) to treat HIV infection dramatically reduced the occurrence of PCNSL in the immune-compromised population[37]. According to one study, the incidence rate of primary and secondary brain lymphomas dropped from 2.8 per 1000 patient-years in 1990 to 0.4 per 1000 patient-years in 1998. PCNSL patients with AIDS are younger than those with intact immune system, and they present with a CD4+ cell count below 50 cells/µl[47].

The clinical presentations include seizures, occurring in 2-33% of cases, infiltration of the wall of the third ventricle results in inappropriate secretion of ADH, diabetes insipidus, hyposexuality, hyperphagia and psychotic thought changes. Tumor infiltration of the brain stem and walls of fourth ventricle, which occur less commonly, may present with dysconjugate gaze, vertigo, ataxia and intractable vomiting. The involvement of the spinal cord resulting in myelopathy is less frequent. The involvement of cranial or peripheral nerve roots causes migratory pain syndromes (referred to as 'neurolymphomatosis')[45]. Intraocular lymphoma is not easily distinguished

from therapy-resistant viritis attributable to sarcoidosis, cytomegalovirus infection or Behcet's syndrome[48].

Diagnosis is by neuro-imaging with multiple lesions seen in 20-40% of patients[45]. More than 98% of PCNSLs are malignant non-Hodgkin's lymphoma (NHL) of the B-cell type. Histo-immunochemistry demonstrates perivascular B cells expressing pan-B-cell markers such as CD19, CD20 or CD79a. A 'reactive' T cell infiltrates recognized by its labeling with anti-CD3 antibodies, is always present (45). Treatment with HAART has markedly reduced the incidence of PCNSL and has increased eligibility for chemotherapy and survival after chemotherapy. Trials are ongoing to evaluate the efficacy of HAART and methotrexate combination in affected patients[49,50].

Cryptococcal meningitis

Cryptococcal meningitis (CM) is the most common life threatening fungal opportunistic infection in HIV infected patients[51]. 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[23-26, 51,52]. In Zimbabwe, CM accounts for 45% of all laboratory-proved cases of meningitis in adults[52]. 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[52]. Although unusual, meningeal symptoms may be seen with CM in 25-30% of patients[51]. 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[52]. Despite treatment, mortality in the acute stage of CM remains high (10%-25%) and the 1 year survival rate is about 30%-60%[51-53]. Many patients seem to have an indolent course even without treatment. The treatment consists of intravenous amphotericin B (0.7 mg/kg/day)[52]. Fluconazole has shown similar rates of treatment success to those of low doses (0.4 mg/kg/day) of intravenous amphotericin B[53].

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). After 2 weeks, this combination may be supplanted by oral fluconazole (400 mg/day) for 8 weeks. This therapy seems very successful (6% of initial mortality and 8% of overall mortality)[53]. Lifelong maintenance therapy is essential to prevent relapse of CM. 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[54]. Unfortunately, in many tropical countries, this antifungal treatment is not available. 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%) (55). 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

Toxoplasmosis encephalitis (TE) is the most common opportunistic infection causing encephalitis or focal cerebral lesions[56]. About 3% to 40% of patients with AIDS will develop TE[56,57]. In tropical countries, the frequency of TE in necropsy series of AIDS patients is high: 34% in Brazil, 23% in Côte d'Ivoire, and 19% in India[53]. Risks factors for TE are a previous Toxoplasma gondii infection and a CD4+ cell count< 100/mm^3 [57]. Geographical differences in TE rates among patients with AIDS may be explained by the worldwide observed variation of Toxoplasma IgG seroprevalence[56]. TE presents with a constellation of symptoms and signs, of which only chorea is thought to be pathognomonic in patients with AIDS. Diagnosis is made on the basis of clinical symptoms and CT or MRI findings (contrast enhancing space occupying lesions of the brain)[57]. In tropical countries where CT is not available, the diagnosis should be made on clinical grounds and fast response to presumptive therapy[53].

The current recommended therapy of TE is a 4 to 8 week course of sulfadiazine and pyrimethamine[58,59]. Adverse reactions to these medications are common, occurring in as many as 25% to 53% of patients[59]. Alternative less toxic medications namely, azithromycin, clarithromycin, atovaquone, and trimethoprim-sulfamethoxazole (TMP-SMZ) are under investigation (60). In an open study that followed up 21 patients who were treated with TMP-SMZ (160 mg trimethoprim and 800 mg sulfamethoxazole three times daily by oral or intravenous route for 4 to 6 weeks) showed clinical and radiological improvements 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[53, 60].

Tuberculosis

One third of the world's population is thought to be infected with Mycobacterium tuberculosis[61]. 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 (61). HIV infection is the strongest risk factor for the progression of latent M tuberculosis infection to active TB[62]. 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[61,62]. TB is a major cause of death in patients infected with HIV worldwide.

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[61,62]. 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[59]. In North American or European studies, CNS TB is unusual and occurs in 5% to 10% of patients infected with HIV[61-63]. 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[64]. In tropical countries, TB meningitis is a relatively frequent complication of HIV infection, and such infection is often undiagnosed. Despite antituberculous drugs, the mortality of TB meningitis remains high[65]. In resource poor tropical countries, antituberculous regimens containing rifampin are often unavailable.

HIV-Associated Myelopathy (HAM)/Tropical Spastic Paraparesis (TSP)

In 1964, a progressive thoracic myelopathy was described in Jamaican adults and this disorder was termed tropical spastic paraparesis (TSP)[66]. In 1985, Gessain et al clarified the aetiology of TSP by reporting in Martinique that 60% of these patients had antibodies to HTLV-1[67]. 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[68]. 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). It has two regulatory genes: the tax gene which is responsible for the activation of viral replication, and the rex gene which, conversely, inhibits replication. Molecular analysis of HTLV-1 strains from the known endemic areas have identified three different genotypes namely[69], widespread cosmopolitan subtype (HTLV-1 subtype A), large central African genotype (HTLV-1 subtype B), and Melanesian subtype HTLV-1 subtype C). In tropical areas, HTLV-1 infection is endemic near the equator. The highest frequency pockets to have been reported include the Caribbean basin, Colombia, and equatorial Africa. 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[70].

HTLV-1 is, however, a mildly infective virus. 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. 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[71]. Finally, patients have developed seroconversion and HAM/TSP in as little as 6 months after transfusion with contaminated blood products.

The most common initial symptom in patients with HAM/TSP is either leg weakness or difficulty in walking[67,68,71]. 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. The frequencies of loss of touch and pain sensations ranges from 27% to 53% of the patients in three major series[72]. HAM/TSP usually presents with an insidious course. However, the evolution of the disease is rapid and aggressive in South Africa and spontaneous improvement has been reported among patients with definite HAM/TSP[73].Whatever the course of HAM/TSP, the clinical impression is that the neurological disability becomes relatively stable a few years after onset[70]. 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 (seen in 15% of affected people) was described among the original patients with HAM/TSP[68,70]. 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[73] 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[74]. Polymyositis or anterior cell degeneration linked to HTLV-1 sometimes develop in the presence or in the absence of HAM/TSP. Finally, the coexistence of systemic symptoms including alveolitis, sicca syndrome, arthritis, and infective dermatitis are the striking features of HAM/TSP.

Common feature is the presence of atypical lymphocytes with convoluted nuclei (flower cells) in the blood of infected patients. 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. Most patients with HAM/TSP also show an intrathecal immune response against HTLV-1 synthetic peptides (especially against HTLV-1 env gp21 synthetic peptides) 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. The most useful neurophysiological parameter seems to be the central sensory conduction time, which correlates well with disability score[73]. 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[70,73]. Frequency of small deep and subcortical white matter, small infratentorial and large periventricular

lesions is lower in HAM than in multiple sclerosis.

Based on the inflammatory nature of the CNS lesions in HAM/TSP, immunomodulatory agents were assessed in this disease. Clinical improvement under immunosuppressive agents such as azathioprine or cyclophosphamide was only marginal. Blood purification or high doses of intravenous immunoglobulins provided no sustained clinical benefits. The dramatic efficacy of high dose vitamin C in a small open trial was not later confirmed. Five out of seven patients treated by IFN- 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[75]. 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- production may be beneficial. 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.

Neuromuscular disorders

Neuromuscular disorders are common and important causes of morbidity[21]. 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 manifestations in tropical countries.

AIDS and Psychiatry

Patients with HIV/AIDS are predisposed to psychiatric disturbances such as adjustment disorders or symptoms of anxiety and depression arising from the distress associated with being diagnosed with the infection and from the implication of the diagnosis. A minority of patients will have major mood disorders and psychotic syndromes which mechanisms are complex and still poorly understood. Severe psychotic symptoms contribute to the difficulties of medical care and require immediate management[76].

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[77]. HIV readily infects the developing CNS of children, and is a major cause of morbidity and contributes to the fatal outcome[77].

Postmortem studies show that most children dying with AIDS have evidence of neurological involvement[78]. Children more often have a HIV encephalitis, and less superimposed infections and lymphoma than adults, particularly children living in tropical countries[79].

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[80]. Other neurological manifestations include stroke [69], extrapyramidal, and cerebellar signs, and peripheral neuropathies[78].

In Africa, perinatal HIV infection is associated with motor and cognitive delay. 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. 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[77, 79].

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