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Low prevalence of progressive multifocal leukoencephalopathy in India and Africa: Is there a biological explanation?

SK Shankar,[1] P Satishchandra,[1] A Mahadevan,[1] TC Yasha,[1] D Nagaraja,[1] AB Taly,[1] S Prabhakar,[2] and A Nath[3]

[1]*Departments of Neuropathology, Neurology, National Institute of Mental Health and Neurological Sciences, Bangalore, India;* [2]*Department of Neurology, Postgraduate Institute of Medical Sciences, Chandigarh, India; and* [3]*Department of Neurology, Johns Hopkins University, Baltimore, Maryland, USA*

Infection with human immunodeficiency virus (HIV) clade C virus is the most common form of HIV infection in the world. It largely infects populations in Africa and Asia and not much is known about the neurological complications associated with the virus. Cases of progressive multifocal leukoencephalopathy (PML) have been rarely reported in the literature in the acquired immunodeficiency syndrome (AIDS) or non-AIDS populations from these regions. In this article, the authors present three recently diagnosed patients with AIDS and PML from one neurological center in India, review the diagnostic challenges faced, and speculate on the possible biological reasons, including viral strain differences as well as HIV and JC virus interactions, that may account for the low incidence. *Journal of NeuroVirology* (2003) **9(suppl. 1),** 59–67.

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Introduction

Human immunodeficiency virus (HIV) infection is rapidly infecting increasing number of people in Africa and South East Asia. According to the World Health Organization (WHO), 28.5 million are infected with HIV/acquired immunodeficiency syndrome (AIDS) in sub-Saharan Africa. In 2001, an alarming 24.8% of pregnant women attending antenatal clinics in Africa were found infected with HIV, highlighting the magnitude of spread to the next generation. In India as on 31st August 2002, a total of 39,742 cases of AIDS were recorded, though possibility of under reporting is high. Inspite of these figures, very little is known about the spectrum of neurological complications of HIV infection in the general population during the course and progression of HIV to AIDS. The predominant strain of HIV in these regions is clade C, unlike in the Western continents where clade B predominates. The large population in these countries would make clade C the most common subtype of HIV infection in the world. Yet no confirmed case of progressive multifocal leukoencephalopathy (PML) is reported in the published literature from this patient population, though clinicians occasionally do entertain the diagnosis based on clinical and imaging features. In this presentation, we review the challenges posed in the diagnosis of this entity and share the experience at the premier Neuropsychiatric Institute, located in South India, where the prevalence of HIV/AIDS is high and make suggestions for future directions of research.

Prevalence and risk factors for HIV infection in India

Data from the National AIDS Control Organization (NACO), Government of India, as of August 31, 2002, shows that HIV infection presenting with AIDS is primarily heterosexual (84.49%) and predominantly in males (75%), occurring mostly in the age group between 15 and 29 years (36%) and between 30 and

Address correspondence to A. Nath, Department of Neurology, Johns Hopkins University, Pathology 509, 600 N. Wolfe Street, Baltimore, MD 21287, USA. E-mail: anath1@jhmi.edu

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44 years (52.5%). The modes of HIV transmission in India were found to be primarily heterosexual (84.49%), followed by perinatal transmission (2.56%), infected blood and blood products (2.97%), and intravenous drug abuse (3.02%). Relevant history was not available in 6.95% of cases. According to the cumulative number of AIDS cases recorded by NACO, cases were maximum in Tamil Nadu—South India (18,276 cases); followed by Maharashtra (8262 cases) and Gujarat (1704 cases)—both in Western India; Karnataka (1498) and Andhra Pradesh (1753)—in Southern India; whereas in Manipur, Northwestern India, with large pool of drug abusers, 1238 cases of AIDS were reported. Centers in North India, New Delhi and Chandigarh, recorded only 702 and 563 cases of AIDS. In Karnataka, the incidence of HIV infection in antenatal clinics was found to be 1.13%, whereas it varied from 0.00% to 0.4% in Chandigarh and the neighboring states of Punjab and Haryana. Similarly the incidence of HIV in sexually transmitted disease (STD) clinics was low in Chandigarh (3.78%) and was significantly high in Karnataka (16.4%). The reason for this regional variability is unclear. Despite routine mandatory screening of the blood in Blood Banks, nearly 3% of cases acquired HIV by blood transfusion.

Neuro-AIDS in India

In a hospital-based study from Assam (a North Eastern state of India), 5808 cases were screened and 84 were found to be seropositive for HIV during the year 2000. These 70 cases were between the ages of 20 and 40 years with male preponderance (79%). Majority of these patients hailed from Manipur, a neighboring state, where drug abuse is rampant. Only two cases had neurological features of tuberculous meningitis (personal communation, Dr.Ajita Mohanta, practicing neurologist, in Guwahati, Assam, working in a private multispeciality hospital catering to all seven states of North Eastern India).

Gupte *et al* (1993) evaluated the spectrum of neurological mainfestations of 132 consecutive HIV-positive/AIDS cases admitted to a multispeciality general hospital in Bombay (Western India) between April 1989 to January 1992. They noted that neurotuberculosis acounted for 58.82% of cases, followed by herpes simplex encephalitis, cryptococcal meningitis, and cerebral toxoplasmosis. Not a single case suggestive of PML clinically, radiologically, or at autopsy was documented (Gupte *et al*, 1993).

In an autopsy study specially recording the profile of central nervous system (CNS) pathology in patients of AIDS, Lanjewar *et al* (1988) from Bombay reported observations on 85 adult brains between 1988 to 1996. Opportunistic infections were observed in 39% of cases (toxoplasma 13%, neurotuberculosis 12%, cryptococcal meningitis 8%, cytomegalovirus encephalitis 6%). Though they noted multifocal myelin loss in 21% and angiocentric pallor in 6% of cases, not a single case of PML was reported based on clinical neuroimaging or pathological grounds.

From Christian Medical College, Vellore, South India, during 1980 to 1992, 61 subjects were diagnosed to have AIDS. Tuberculosis was the most common opportunistic infection (52%) and two patients had CNS involvement. No case of PML was recorded even at this centre (Chacko *et al*, 1995).

In 1981, one case of PML was diagnosed in a nonimmunocompromised, non-HIV adult at autopsy. The diagnosis was based on histological features in brain (personal communication from Prof. Chitra Sarkar, Department of Pathology, All India Institute of Medical Sciences, New Delhi). Subsequently, another case of PML was reported in a renal transplant recepient from G. B. Pant Hospital, New Delhi (personal communication, Prof. Medha Tatke, Department of Pathology). The diagnosis was established by histology and electron microscopy. Both cases were HIV-seronegative individuals.

At National Institute of Mental Health and Neurosciences (NIMHANS), a neuropsychiatric hospital located in South India, the seropositivity for HIV at the Surveillance Centre located in the Institute has risen from 1% in 1989–1992 to 16.8% in the year 2000—a steep rise noted from 1996 (12.8%) onwards. Four hundred twenty-seven cases of HIV with neurologic manifestations were evaluated clinically between 1989 and 2000 (Nalini *et al*, 2001). CNS complications were noted in 408 (95.5%) cases and peripheral nervous system involvement in 19 cases (4.5%). Opportunistic infections were detected in 381 (93.5%) cases while 27 cases (6.5%) had neurological manisfestations without AIDS. Neurotuberculosis topped the list (120 cases), followed by cryptococcal meningitis (99), toxoplasma encephalitis (36), neurosyphilis (7), staphylococcal meningitis (1), meningococcal meningitis (1), herpes zoster (5), and herpes simplex encephalitis (1). Polymicrobial opportunistic infections included combinations of tuberculous meningitis (TBM), toxoplasma encephalitis, cryptococcal meningitis, and acanthamoeba encephalitis. During the period 1989–2000, three cases of PML (0.7%) were diagnosed based on clinical and neuroimaging features in HIV-positive individuals but was not authenticated by pathology.

At NIMHANS, to date 111 HIV-positive cases have been autopsied and the brains have been examined to characterize the pathological lesions, with special reference to opportunistic infections. Cryptococcal meningitis, toxoplasmosis presenting as mass lesions or encephalitis, and tuberculous meningitis were the most, common opportunistic infections (Table 1). In one case, based on neuroimaging features, possibility of PML involving brainstem was entertained, but pathological examination revealed toxoplasma encephalitis. During the past $1^1/_2$ years, three histopathologically and

Table 1 Postmortem diagnosis of patients with neuro-AIDS ($n = 111$) (1990 to July 2002)

Diagnosis	*No. of patients*
Cryptococcal meningitis (CM)	36
Toxoplasma encephalitis (TE)	24
Tuberculous meningitis (TBM)	18
CM + TBM	06
CM + TE	07
CM + CMV encephalitis	01
TE + TBM	06
TE + acanthameba encephalitis	01
CM + TBM + TE	01
Herpes simplex encephalitis	01
Meningococcal meningitis	01
Lymphoma	01
HIV leukoencephalitis	03
Lymphomatoid granulomatosis	01
PML	02
Cerebral malaria	01
ADEM	01

immunohistochemically confirmed cases of PML were diagnosed. Two other cases of PML in patients with HIV infection have been reported in the published literature from India (Chadha *et al*, 2000; Kakar *et al*, 1998), whereas from sub-Saharan Africa, not a single case of PML is reported in the literature, to the best of our knowledge.

Diagnostic challenges

Because most people are infected with JC virus in childhood, serum titers are usually not very helpful. Demonstration of the virus in the brain or the cerebrospinal fluid (CSF) is necessary. Diagnosis of PML requires access to magnetic resonance imaging (MRI), brain biopsy, or detection of viral DNA by polymerase chain reaction (PCR) in the CSF. Some of these techniques are not readily available in these countries. Autopsies are also not regularly performed on patients who die with AIDS due to lack of appropriate facilities, and when performed, may be after several days and brain may not be removed because of difficulties of cutting through bone and apprehension of sustaining injuries from bone chips and sharp instruments used for cutting bone. Even with access to all the above techniques, diagnosis of PML can sometimes be difficult, because occasionally there may be an associated immune reaction leading to contrast enhancement on MRI (Post *et al*, 1999; Thurnher *et al*, 2001) or small amounts of inflammatory infiltrates on histology. Access to antiretroviral agents have led to the emergence of an entity of leukoencephalopathy associated with immune reconstitution that may resemble PML neuroradiologically (P. Cinque, personal communication). HIV leukoencephalopathy may also be mistaken for PML. Hence confirmation of diagnosis by histopathology requires demonstration of virus by electron microscopy, immunohistochemistry, or *in situ* hybridization.

PML cases at NIMHANS

Within the past 1 year (2000–2001), three cases of PML were seen at NIMHANS. Prior to this, no cases of PML were recorded either in the AIDS or the non-AIDS patients. These cases illustrate the diagnostic challenges faced in establishing a diagnosis of PML. Case 1 was a 30-year-old woman with progressive weakness of both legs for 1 month associated with severe vertigo, dysphonia, dysarthria, and hesitancy of micturition for 2 weeks. On admission, she had bilateral VI, VII, IX, and X cranial nerve involvement and hypotonia of all the limbs. She had grade III power (MRC grade) in the legs, with extensor plantar responses. On fundoscopic examination, the left optic fundus had blurred margins, whereas the right was normal. Her vital signs and routine hematological and biochemical investigations were normal, but for raised erythrocyte sedimentation rate (ESR) (Westergren 80 mm/1 h). Tests for syphlis, toxoplasma, mycobacteria, and cryptococcus in both serum and CSF were negative. Chest radiographs were normal. MR imagimg of the brain revealed hypointense lesions on T_1-weighted images in mid pons extending to superior and middle cerebellar peduncle, cerebellar white matter, and pontomedullary junction, that were hyperintense on T_2-weighted images—contrast studies were not carried out. With a provisional diagnosis of postinfectious acute disseminated encephalomyelitis (ADEM) involving the white matter of brainstem or brainstem encephalitis, she was treated empirically with antituberculous and antitoxoplasma regimen with steroids. During the course in the hospital, repeat MRI revealed multiple hypointense lesions in subcortical white matter in addition to those in brainstem, which had remained unchanged. She progressively developed dysphagia, dysphonia, quadriplegia, and respiratory distress and succumbed 27 days after admission. Autopsy confined to examination of the brain alone, was conducted 3 h post mortem. She was detected to be HIV-1–seropositive post mortem, possibly transfusion related, as she had undergone a hysterectomy 2 years back and received 10 units of blood transfusion.

On gross examination of the brain, the left optic radiation was found softened and discoloured, extending to the striate cortex. From the pontomesencephalic junction to pontomedullary junction, the white fiber tracts were softened and granular. The pathology had extended to cerebellar peduncles, maximally involving middle cerebellar peduncle and cerebellar white matter. Histological examination of the brain stem revealed demyelinating lesions. In these areas, enlarged oligodendroglia with basophilic inclusions and abnormally hypertrophic, 'tumor-like' astrocytes were seen (see Figure 2).

Case 2 was a 48-year-old woman with a history of fever for 4 days followed by diplopia of acute

onset and diminished vision, $1^1/_2$ months prior to hospital admission. She also had difficulty in walking due to fatigue and fear of falling. She had undergone hysterectomy 10 years ago for dysfunctional uterine bleeding. Examination on admission revealed a visual acuity of 6/36 in both eyes and a normal ocular fundus. Power, tone in limbs, and cerebellar function was normal with no sensory deficit. Deep tendon reflexes were brisk bilaterally and plantar was flexor. Gait was ataxic. Routine hematological examination revealed raised ESR (64 mm/1 h Westagren), mild lymphopenia (9% to 14% lymphocytes), and relative polymorphonuclear leucocytosis. Renal and liver function tests were normal. She was found to be HIV-1 seropositive. Lumbar CSF was clear, with normal values of protein, sugar, and cells. Immunoglobulin G (IgG) immune complexes to mycobacteria were detectable in the CSF, but was negative for antibody to mycobacteria, cryptococci, and toxoplasma. CSF and serum (Venereal Disease Research Laboratory) was negative. Ultrasonography of abdomen and duodenal biopsy were normal. Endoscopy showed esophageal candidiasis and kidney biopsy showed interstitial nephritis. MRI of the brain revealed widespread, multiple nonenhancing lesion in upper mid brain, pons, bilateral, and subcortical white matter bilaterally. Visual, somatosensory, and auditory evoked potentials were abnormal. Nerve conduction studies showed a mild-to-moderate sensory neuropathy. Clinical differential diagnosis included postinfective or paraneoplastic acute disseminated encephalomyelitis, CNS vasculitis, or brainstem encephalitis. She received methyl prednisolone 1 g/day for 5 days. She developed dysathria 10 days after admission and slowly became disoriented. She developed bronchopneumonia and succumbed 45 days after hospitalization. Gross examination of the brain revealed left frontal pole atrophy with sulcal prominence. White matter softening was noted bilaterally, though asymmetric, involving corona radiata, corpus callosum, optic radiation, internal capsule, left middle cerebellar peduncle, and right pontine tegmental white matter. Histology revealed classical features of PML involving the white matter and extending to the grey matter along the radiating fiber tracts.

Case 3 was a 30-year-old male, chronic alcoholic, smoker, a manual laborer by profession, and father of three children. He presented with fever and cough with expectoration 3 months back. He was diagnosed to have pulmonary tuberculosis and received antituberculous therapy. During the course, he was detected to be HIV positive, as also his spouse. They received psychological counseling but no antiretroviral therapy was provided. He was referred to Neurology Services of NIMHANS as he complained of insidiously progressive right lower limb weakness with inability to walk of 3 weeks' duration, and dull headache for 1 month. On examination, he had no cognitive deficit but was confused and withdrawn. Muscle power in lower limbs was 4/5 and normal in the upper limbs. All deep tendon tendon reflexes were brisk, but plantar responses were flexor. Routine hematological and biochemical tests were within normal limits, but for raised ESR (72 mm/1 h Westergren). Lumbar CSF had marginally raised protein (62 mg%) and pleocytosis (120 cells/mm^3; 98% lymphocytes). CSF and serum were negative for toxoplasma, cryptococcal, and mycobacterial antibody or antigens. Cranial computed tomographic (CT) scan showed hypodense lesion in right parietal region and MRI revealed multiple deep white matter, paraventricular lesions, in the right parietal zone. There was no evidence of compressive myelopathy. Electromyography (EMG) revealed features of axonopathy of common peroneal nerve bilaterally with absent F waves, suggestive of proximal demyelination. With a radiological diagnosis of a deep seated glioma/neoplastic lesion in an immunocompromised individual, steriotaxic biopsy was done to establish the diagnosis. Postoperative CT scan showed another hypodense lesion in the right frontal region (Figure 1). Postoperatively, the clinical condition was essentially same, with no deficits. The antituberculous therapy, was continued, in view of diagnosis of pulmonary tuberculosis. Two days later, he developed a foot drop on the right, hemiparesis on the

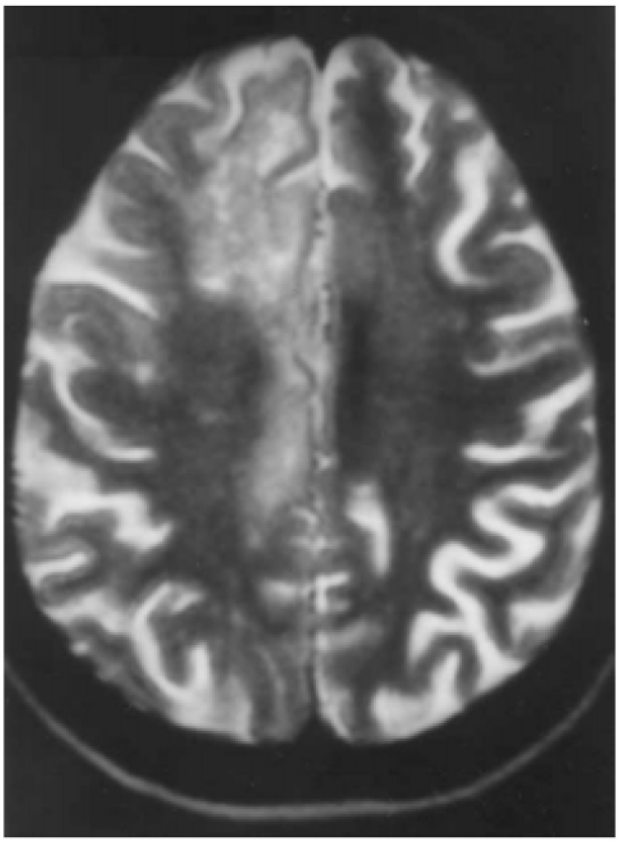

Figure 1 MRI of case 3 showing hyperintense white matter lesions in superior longitudinal fasciculus on T2-weighted images.

left, and persistent headache. Histological examination confirmed the diagnosis of PML. Patient was discharged in December 2001, with advice to continue antituberculous therapy and antiedema measures and referred back to his treating physician. No further follow-up was available.

Immunostaining with cross-reactive polyclonal antibody to JC virus (donated by Dr. Naota Aoki, Division of Pathology, Department of Toxicology, Tokyo Metropolitan Research Lab of Public Health, Hyakunincho, Shinjukuku, Tokyo 169; antibody dilution 1:500), highlighted the oligodendroglial inclusions. In addition, the viral antigen was found in large tumor-like astrocytes and neurons in the lower layers of the cortex. In the white matter, in focal areas especially in the perivascular zones, the antigen was present as diffuse, irregular plaques with long processes. These features were consistently found in all the three cases (Figure 2).

Electron microscopy of the brain in one of the cases revealed characteristic aggregates of viral particles in the nuclei. The immunohistochemical and and ultrastructural studies confirmed the diagnosis. Facilities for serological tests and PCR are not available in India at present.

These three cases are illustrative of the challenges faced in diagnosing PML in less industrialized countries such as India and regions of Africa. Due to the low incidence of PML and lack of awareness, it is often not considered in the differential diagnosis. The patients may not have any obvious risk factors for HIV infection. Further, PML may be the presenting symptom of HIV infection. In the first two cases, the diagnosis of PML was made only at autopsy. In case 3, the pleocytosis in the CSF with active pulmonary tuberculosis complicated the clinical presentation.

Reasons for low incidence of PML

Underdiagnosis or underreporting of cases

As is evident from the above cases, the clinical diagnosis of PML was missed in all three patients. ADEM was considered the most likely cause of the

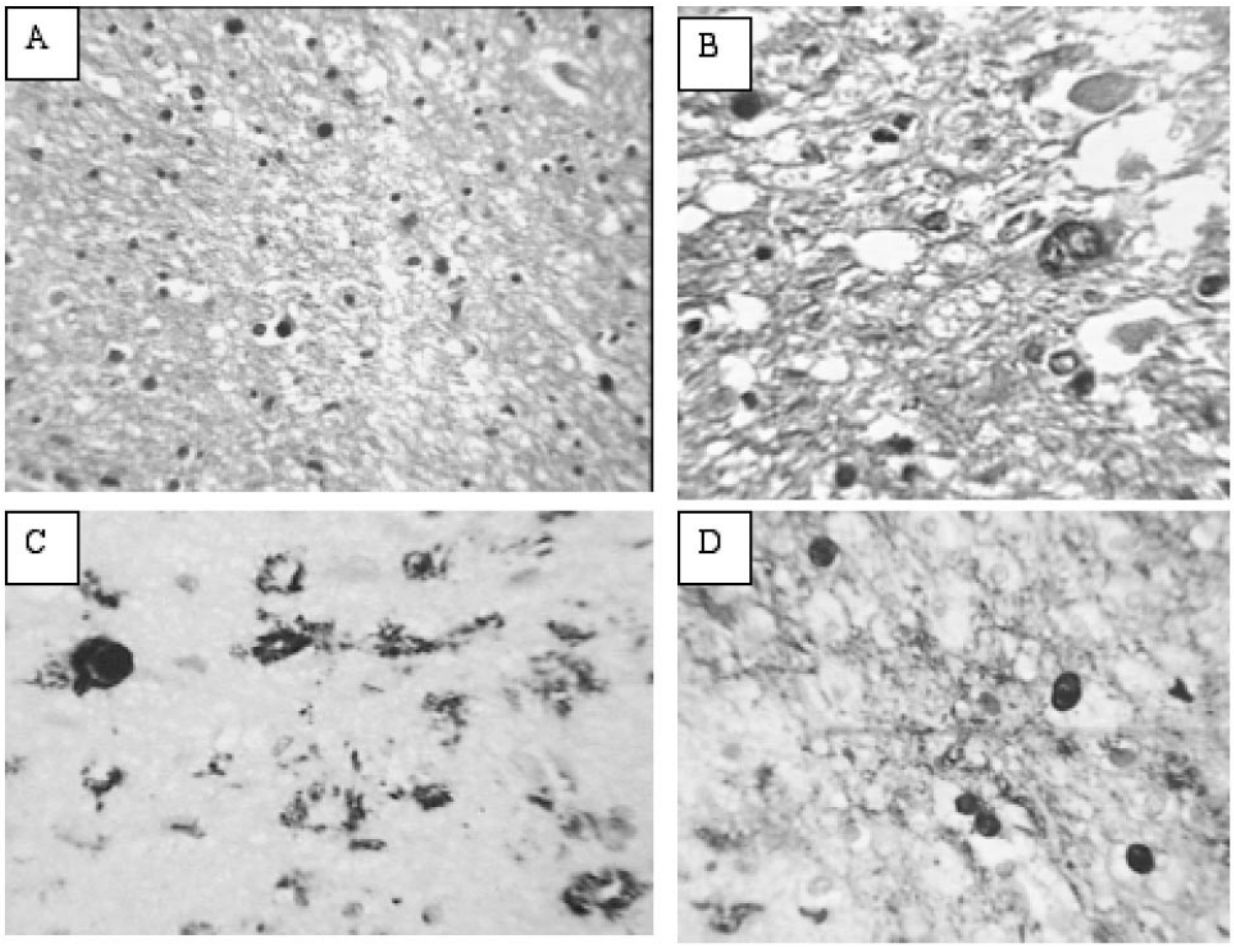

Figure 2 Histopathological observations in patients with PML. (**A**) Oligodendroglial inclusions in demyelinated area. Hematoxylin and eosin stain; magnification: 320×. (**B**) Oligodendroglial inclusions (*arrows*) and tumor-like astrocyte. Hematoxylin and eosin stain; magnification: 320×. (**C**) Immunolabelling for JCV in oligodendroglial inclusions and the glial elements in the neuropil. Magnification: 320×. (**D**) Immunolabelling for JCV in neurons and glia in the lower layers of the cortex. Magnification: 320×.

disseminated lesions, followed by vasulitis. In fact, the first two cases received a course of steroids without benefit. In the first two cases, the risk factors for HIV infection were also not readily apparent. In the first case, HIV infection was recognized only at autopsy. It is thus possible that other cases have similarly been missed. Low autopsy rates in different centers may further contribute to the underdiagnosis of PML. It is also likely that suspected cases of PML may have not been reported as the confirmatory tests were not readily available in India.

Death due to other causes

PML usually occurs in patients with very severe immunosuppression, although occasionally it may occur as a presenting manifestation of AIDS (Berger and Major, 1999). Other opportunistic infections, particularly pulmonary tuberculosis usually occur at higher CD4 cell counts. Hence one possibility is that patients may die from other opportunistic infections before they get a chance to develop overt PML.

Nonvirulent strains of JCV

Significant genomic diversity of JCV has been identified in various geographical regions around the world (Guo *et al*, 1996; Suzuki *et al*, 2002). The majority of JCV strains in India and Africa are similar, although some regions of India have several other strains of JCV as well (Saruwatari *et al*, 2002). Laboratory studies show that some strains of JCV infect glial cells more readily than others, hence it is likely that similar differences in virulence of JCV strains may occur between the genotypes in different geographical regions. However, this is an area that requires further investigation.

Differences between interactions of JCV and HIV clades B and C

In Africa and southern India, there is also a decreased prevalence of Kaposi's sarcoma and HIV encephalitis. Because the HIV Tat protein has been shown to play an important role in the pathogenesis of all of these complications of AIDS, one possibility might be that the HIV clade C virus Tat is not as potent as HIV clade B virus in its interactions with human herpes virus (HHV-8), the etiological agent of Kaposi's sarcoma, in causing neurotoxicity and microglial cell activation to mediate HIV encephalitis or in its interactions with JCV to cause pathology. We carried out a comparison of sequence diversity of the regulatory region and the nuclear localization region of Tat amongst HIV clade C strains from India (Lole *et al*, 1999) and Africa (Novitsky *et al*, 1999) with HIV clade B strains from the published literature. Even within clade B, when we chose Tat sequences from HIV-demented patients, which had considerable sequence diversity (Mayne *et al*, 1998), we found that the clade C sequences were distinct, suggesting that likely these variations would be important for dictating functional properties of the clade C viruses. However, functional

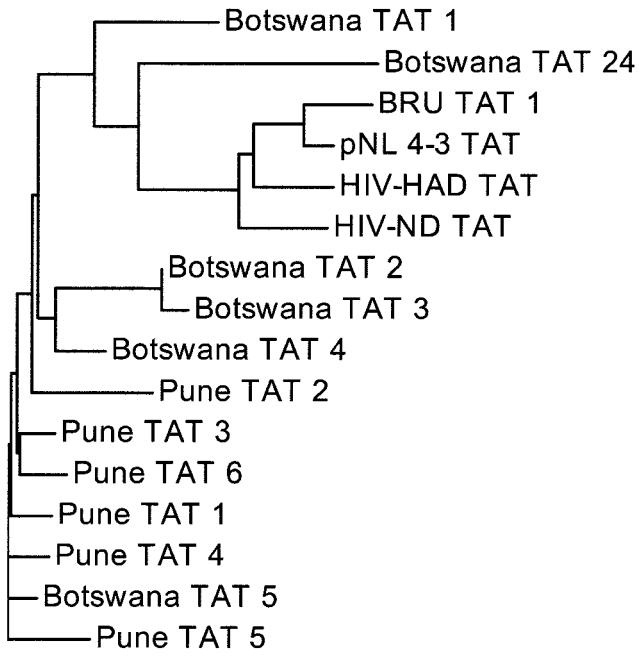

Figure 3 Divergence of published HIV Tat (first exon; amino acids 1–72) sequences from Pune India and from Botswana in Africa. Large differences are noted with clade B sequences using prototypic NL4-3 as an example. Even when compared to Tat sequences from HIV demented (HIV-HAD) and nondemented patients (HIV-ND) important differences, the clade C Tat sequences fall into a separate group.

studies are necessary to validate the significance of these observations (Figure 3). The ability of HIV-1 Tat protein and JCV T antigen in inducing transcription from the JCV late promoter, JCVL, were compared. A JCVL promoter–chloramphenicol acetyltransferase plasmid (pJCL-CAT) was transfected into human glial cells, either alone or together with plasmids producing T antigen and Tat protein. CAT enzyme activity obtained from the transfected cells indicated that both JCV T antigen and HIV-1 tat proteins stimulated JCV late gene expression. However, the level of induction mediated by Tat protein was significantly higher than that obtained with T antigen (Chowdhury *et al*, 1990).

A specific RNA sequence located in the leader of all HIV-1 mRNAs termed the transactivation response element, or TAR, is a primary target for induction of HIV-1 long terminal repeat activity by the HIV-1–derived transregulatory protein, Tat. JCV contains sequences in the 5′ end of the late RNA species with an extensive homology to HIV-1 TAR. Site-directed mutagenesis studies show that critical G residues required for the function of HIV-1 TAR that are conserved in the JCV TAR homolog play an important role in Tat activation of the JCV promoter. In addition, *in vivo* competition studies suggest that shared regulatory components mediate Tat activation of the JCV late and HIV-1 long terminal repeat promoters. These results suggest that the TAR homolog of the JCV late promoter is responsive to HIV-1 Tat induction and

thus may participate in the overall activation of the JCV late promoter mediated by this transactivation (Chowdhury *et al*, 1990, 1992). Further, JCV activation at transcriptional level is mediated by interaction of several inducible regulatory proteins, such as nuclear factor kappa B (NF-κB), C Jun/Ap-1, and NF-1 (Amemiya *et al*, 1989, 1992; Wortman *et al*, 2000). These regulatory proteins can be induced by HIV Tat protein in microglial cells or by cytokines that are induced by HIV proteins in microglial cells (Atwood *et al*, 1995; Chen *et al*, 1997; Conant *et al*, 1996). The elusive behavior of Tat protein to enter into other cells as well as to induce production of cytokines may thus make the JCV dormant in oligodendrocytes or astrocytes target for activation and may be involved in the neuropathogenesis of PML in patients with HIV infections.

There are other mechanisms of interactions between HIV and JCV that could be strain dependent. HIV infection induces a wide variety of cytokines, chemokines, and adhesion molecules in the brain (Merrill *et al*, 1992; Nottet and Gendelman, 1995; Persidsky *et al*, 1997). There is also an upregulation of interleukin (IL-8), RANTES, and several chemokine receptors in astrocytes following infection by HIV. Increased expression of these chemokines along with their receptors would not only have the effect of attracting monocytes and lymphocytes into the brain, but also establish an autocrine/paracrine loop for further activation of astrocytes that may contribute to the inflammatory state in the brain (Cota *et al*, 2000). The mechanisms by with HIV causes an inflammatory response is not fully understood. However, some of the HIV proteins have been implicated in mediating such responses. HIV Tat–derived peptide, when injected into rat brain, increased levels of proinflammatory cytokines (Philippon *et al*, 1994). Our *in vitro* studies show that Tat induces tumor necrosis factor (TNF)-α and IL-1 in monocytes/macrophages and IL-6 in astrocytes. In fact, Tat was more potent than even lipopolysaccharide (LPS) in inducing TNF-α production (Chen *et al*, 1997). Cytokine induction in both cell types is NF-κB dependent (Chen *et al*, 1997; Conant *et al*, 1996; Nath *et al*, 1999). The role of these cytokines in Tat-mediated neurotoxicity remains to be determined. Tat also induces monocyte chemoattractant protein (MCP)-1 expression in astrocytes and the levels of this chemokine are elevated in the CSF and brains of patients with HIV dementia .(Conant *et al*, 1998). We have also shown that Tat induces the transmigration of monocytes across an *in vitro* blood-brain barrier model. This Tat-induced transmigration can be blocked with antisera to MCP-1 (Weiss *et al*). Gp120, the envelope protein of HIV, can also cause cytokine induction in monocytes (Zembala *et al*, 1995) and glial cells (Ilyin and Plata-Salaman, 1997).

Interactions between HHV-6 and JCV

HHV-6 is typically considered a ubiquitous, commensal, and usually benign beta-herpesvirus. However, a high association of HHV-6 infection has been shown in PML lesions and HHV-6 has also been colocalized in JCV-infected cells in the brain (Mock *et al*, 1999). HHV-6 predominantly infects oligodendrocytes (Blumberg *et al*, 2000) and has been also associated with multiple sclerosis. Because both PML and multiple sclerosis are present in low frequency in Asia and Africa, the possibility that differences in HHV-6 strains in these geographical regions may exist and their interactions with JCV need to be explored.

Host genetic differences in development of PML

In Western countries, there also seem to be racial differences in the development of PML. Curiously, there is a higher degree of prevalence of PML in white males compared to African American males (Holman *et al*, 1998). We found that genetic polymorphisms in p53 may account for susceptibility to PML in AIDS and non-AIDS patients (Power *et al*, 2000). Genetic differences in host susceptibility have been well documented for a number of other infectious diseases. It is hence reasonable to postulate that similar differences in host susceptibility might exist for JCV infection as well.

In summary, the incidence of PML is extremely low in regions of the world afflicted by HIV clade C virus. In these regions, even though the diagnosis of PML may be underreported and the diagnosis of PML poses unique challenges; other biological causes for the low incidence of PML need to be considered. These may include differences in viral strains and variability in host susceptibility. Further clinical and molecular biological studies are necessary to determine the true cause(s) of this interesting paradox.

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