Neuropathology of HIV/AIDS with an overview of the Indian scene

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Neurological manifestations of HIV infection and AIDS are being recognized with a frequency that parallels the increasing number of AIDS cases. Next to sub-Saharan Africa, India has the second largest burden of HIV related pathology, essentially caused by HIV-1 clade C in both the geographic locales, in contrast to USA and Europe. But the true prevalence of HIV related neuroinfections and pathology is not available due to inadequate medical facilities, social stigma and ignorance that lead to underdiagnosis. Neurotuberculosis, followed by cryptococcosis and toxoplasmosis in various combinations are the major neuropathologies reflecting the endemicity and manifesting clinically by reactivation of latent infection. Discordance in the clinical prevalence of various infections, when compared to pathological studies highlight similarities in clinical, radiological modalities of diagnosis and inherent problems in establishing definitive diagnosis. Viral infections appear to be relatively rare. Inspite of heavy burden of HIV/AIDS, HIV associated neoplasia is infrequent, including primary CNS lymphomas. HIV encephalitis and HIV associated dementia are considered infrequent, though systematic studies have just been initiated in various centres. Peripheral neuropathy characteristically manifests with vasculitic neuropathy while diffuse infiltrative lymphocytosis syndrome (DILS) involving nerves has not been reported from India. Spinal cord pathology including vacuolar myelopathy is rare, even in asymptomatic cases. Till now the AIDS cases in India were drug naïve but a new cohort of cases following initiation of HAART therapy as a national policy is soon emerging, altering the biology and evolution of HIV/AIDS in India. Lacunae in the epidemiology, diagnosis and study of biology of HIV/AIDS are outlined for future research.

Key words Clade C - cryptococcal meningitis - HIV/AIDS - neuropathics - neuroinfections - neuropathology - toxoplasmosis - tuberculosis

The acquired immunodeficiency syndrome (AIDS) caused by a retrovirus variously termed the human immunodeficiency virus-1 (HIV-1), HTLV III or Lymphadenopathy associated virus (LAV), is no longer a rare or exotic disease. Since its first description in June 1981 it is now a worldwide pandemic. The World Health Organization (WHO) estimates that there are 40 million people in the world infected with HIV. Approximately 95 per cent of these cases as well as deaths from AIDS occur in the developing world. However, autopsies are rarely performed in the developing countries on patients with HIV infection, hence our current understanding of the pathology and pathophysiology of HIV infection largely stems from studies of populations infected with HIV cladeB virus in North America and Western Europe. Of the various subtypes of HIV, subtype C is responsible for >50 per cent of all HIV-1 infections

causing rapidly growing epidemics in India, China, Brazil, and southern and eastern parts of Africa. HIV-clade C therefore infects the largest populations in the world. The subtype distribution in India was confirmed to be predominantly clade C in a study that employed a subtype-specific PCR[1]. Although important sequence differences have been identified in functional domains between the clades, whether these differences translate into alteration in spectrum of pathological manifestations remains unknown. Pathological manifestations are also influenced by host genetic factors and environmental factors unique to developing countries. Hence a comparative analysis of the pathological manifestations from different regions of the world is necessary. Since antiretroviral drugs have only recently been introduced in the developing countries, and only in very select populations, we have compared the neuropathological findings of patients in India with the published literature from the pre-highly active antiretroviral therapy (HAART) era.

In the early years of the epidemic, nervous system involvement was not widely recognized. It is now recognized that every level of the neuraxis can be involved and at least one third of patients with advanced HIV infection will develop neurological complications during the course of their illness[2,3], and in 10 per cent of cases neurological problems may be the first sign of development of AIDS. But at autopsy, more than 80 per cent of patients show evidence of cerebral pathology ranging from HIV encephalitis, opportunistic infections or lymphomas and one half will have some evidence of peripheral neuropathy[4-6]. These figures hold true in countries with limited or no access to antiretroviral drugs[7,8] as well as in those countries with full access to such drugs.

There is virological and clinical evidence to show that the HIV is both lymphotropic and neurotropic.The virus is both genetically and morphologically related to visna, a retrovirus that affects sheep and is both neurotropic and lymphotropic. Secondly the HIV viral particles were recovered from cultures of cerebrospinal fluid (CSF), brain and spinal cord[9]. The levels of HIV specific IgG are higher in CSF than in serum implying active CNS infection. Evidence of low grade infection of the CNS can be demonstrated in asymptomatic individuals within two years of seroconversion who show pleocytosis, positive viral culture or a rise in IgG[10].

Autopsies of patients at this stage reveal abnormalities in 90 per cent of which the commonest is an encephalitis in the absence of any cause other than the HIV virus itself. Clinical evidence for a direct role of the virus in neurological involvement is seen in the appearance of meningitis at the time of seroconversion. Viral sequence studies from the brain now suggest that it may evolve within the brain and it may thus act as a reservoir for the virus[11-13].

The immune deficiency produced by the virus makes patients susceptible to a plethora of opportunistic infections that range from viruses, fungi, parasites and a host of other pathogens newly recognized or previously never considered significant. In addition, the impairment of humoral as well as cell mediated immunity alters the normal inflammatory response to pathogens which translates clinically as minimal signs of inflammation such as fever or meningism, minimal pleocytosis in CSF even in the presence of infection and defective antibody production making diagnostic tests (that employ antibody testing) of little use in diagnosis of infections. The tissue response too is muted which alters brain imaging characteristics and contrast enhancement. Multiple pathogens can simultaneously cause infections further complicating diagnosis and treatment. In the presence of immunosuppression, relapse is common and hence antimicrobial prophylaxis needs to be lifelong.

Opportunistic infections (OI) are the most important and common cause of mortality in HIV infected individuals. Direct HIV infection of the CNS also causes important clinical syndromes like AIDS dementia complex (ADC), HIV encephalitis and encephalopathy with minor and major cognitive abnormalities. The CD4 cell count is a good predictor of the likelihood of the specific disorders and virtually provides a "time of reference" for prediction. Opportunistic infections complicate the late stages of HIV infection. In the early stages, conditions in which there is a prominent inflammatory response such as acute inflammatory demyelinating polyneuropathy, and polymyositis are more common.

Though AIDS is fundamentally the same disease all over the world, the spectrum of opportunistic infections that occur is governed to a large extent by

the endemicity of microorganisms prevalent in the environment. Numerous microbial infections occur with increased efficiency of transmission in the background of HIV that includes bacterial, fungal, parasitic and viral infections. Of these, only the common opportunistic infections prevalent in India are discussed here.

Fungal infections

Fungal infections involving the brain in the vast majority are secondary to a primary focus elsewhere, most often in the lungs or intestine. But the primary focus remains unrecognized in most of the cases, and the only evidence of infection at the time of presentation would be in the nervous system.

Cryptococcal meningitis (CM): Among the fungal infections affecting the CNS, CM due to *Cryptococcus neoformans* is the most common HIV associated complication both in developed and developing countries[14-16]. Signs and symptoms of CNS cryptococcal infections are often subtle and nonspecific, evolving over days or weeks with often only a mild headache as the presenting manifestation. Focal neurological deficits, signs of meningeal irritation and papilledema may be lacking and radiological investigations including computed tomography (CT) and magnetic resonance imaging (MRI) non-contributory. The importance of being alert to this condition lies in the fact that it is easily treatable and diagnosis requires only a simple examination of CSF to demonstrate the budding yeast forms of the fungus. But if the diagnosis is missed, the patient can deteriorate rapidly within hours to days. A clinical aphorism often stated is that headache in advanced HIV disease is cryptococcal meningitis until proved otherwise. Cryptococcal meningitis complicates AIDS when the CD4 counts fall below 100 cells/ul. Sex, race and other opportunistic infections do not significantly alter the risk of CM in HIV patients[15].

Approximately 5-10 per cent of HIV infected patients will develop CM as an AIDS defining illness[17], and in about 40 per cent patients, it may be the initial manifestation of HIV infection[18]. There is however, a wide geographic variation from 2 per cent in Northern Europe to 20-30 per cent in Africa and South East Asia[19]. In a preliminary analysis of 588 cases of HIV infection (from 1990-2002) at the Neurological services, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, south India, cryptococcal infection was detected in 25 per cent of cases, preceded by neurotuberculosis (30%), with both cryptococcus and tuberculosis co-existing with toxoplasmosis in 12 per cent of cases (Satishchandra P, unpublished data). Another clinical series from western India reported cryptococcal meningitis in 67.4 per cent of cases and tuberculous meningitis (TBM) in 18.6 per cent of cases[20].

On the other hand, in an autopsy series of 134 cases (between 1990-2004) from NIMHANS, cryptococcal infection of nervous system topped the list accounting for 31.3 per cent cases, followed by toxoplasmosis (20.8%) and tuberculous meningitis in 20.1 per cent of cases as monomicrobial infections (Shankar SK, unpublished data). The discrepancy between the clinical and autopsy data could be attributable to systemic cryptococcal infection masquerading clinically and radiologically as mycobacterial infection and the clinical bias because of endemicity. Recognition of the entity of 'cryptococcal primary complex' similar to *Mycobacterium tuberculosis* infection can provide an insight into the biology of this infection. It is likely that cryptococcal meningitis in cases of HIV could be reactivation of the dormant lesion in the lung similar to Ghon's focus of pulmonary tuberculosis.

The fungus is a common soil contaminant being excreted in feces of several birds particularly pigeons. In HIV patients as well as in other immunocompromised states, cryptococcal infection is caused almost exclusively by the neoformans variant. Infection occurs via inhalation and primary infection is localized to the lung from where there is dissemination to other organs including brain. The resulting lung infection is usually asymptomatic. Spread to the brain most often causes leptomeningitis very similar to tuberculosis. The CSF facilitates establishment of infection because it lacks complement and immunoglobulins and thereby acts as a good culture medium for the fungus. CNS involvement by the fungus causes a leptomeningitis and uncommonly a meningoencephalitis. Cryptococcomas (localized granulomas) are extremely rare.

In addition to nonspecific clinical complaints like fever, altered mental status, nausea and vomiting, and severe headache, elevated intracranial pressure (ICP) is reported in excess of 50 per cent of HIV-1 infected patients with CM[21] without accompanying hydrocephalus or cerebral oedema. A retrospective study of 119 cases of *Cryptococcus* with HIV from NIMHANS, south India, the cranial CT scanning revealed features of cerebral atrophy in 19 per cent and hydrocephalus in 10 per cent of cases (unpublished data). In the study from NIMHANS, nearly 90 per cent of cases of cryptococcal meningitis manifested with "unbearable headache" with or without mild fever resembling acute subarachnoid haemorrhage. The severe headache abated spontaneously after two to three weeks of antifungal therapy, but did not respond to mannitol and steroid therapy suggesting pathogenetic mechanisms other than cerebral oedema is responsible for the headache (Satishchandra P, unpublished observations). Saag *et al*[21] emphasized that elevated intracranial pressure has been reported in excess of 50 per cent of HIV-1 infected patients with CM but in the absence of accompanying hydrocephalus or cerebral oedema. An opening CSF pressure of 250-350 mmH$_2$O has been recorded[22]. Importantly, clinical signs of raised intracranial pressure were absent even in those patients with highest pressures. The pathophysiology of this increased ICP in the absence of associated clinical signs has not been fully elucidated[17]. A preliminary pathological study of the brain and the dural venous sinuses in our autopsied cases (unpublished data) revealed plugging of the arachnoid villi by masses of cryptococci, at places almost occluding the venous sinuses. This could be responsible for impendence to CSF circulation leading to dynamic hydrocephalic attacks, not recognized in cranial CT scan or MRI in majority of instances.

Pathological examination of the brain in cryptococcal meningitis typically shows mucinous exudates covering the superolateral aspect of the brain, unlike the basal exudates of tuberculous arachnoiditis. It also produces multiple cystic non-granulomatous parenchymal lesions in basal ganglia and thalamus, and the cortical ribbon, which suggest haematogenous spread of the fungus and entrapment around the endarteries of the pial, lenticulostriate and thalamostriate vessels especially with relatively long duration of illness. Inflammatory response to the fungus is characteristically sparse as the capsule of the cryptococci inhibit phagocytosis and impair leukocyte migration[23]. Giant cell reaction to the cryptococci or granulomatous reaction to produce cryptococcomas are not often seen. Rarely large plaque like demyelinating lesions resembling progressive multifocal encephalopathy (PML) on imaging and gross pathology are seen. This probably represents dispersal of the organisms along the medullary veins, following blockage of superior sagittal sinus and venous impedence.

Of the diagnostic modalities available, cryptococcal antigen in CSF and serum is virtually always positive except in very early stages of the disease or in cryptococcomas. Sensitivity of India ink test on CSF is approximately 70 per cent[24]. Fungal culture is useful only for speciation of the organism and sensitivity to antifungal agents.

In a comparative study of cryptococcal meningitis with and without associated HIV from our centre[25], it was noted that poor CSF inflammatory cell response, positive culture of cryptococci from extraneural sites and systemic dissemination are common when associated with HIV infection and connote a poor prognosis. Clinical indicators of poor prognosis include depressed level of consciousness, development of signs of raised intracranial tension, markedly depressed CSF glucose, CSF white cell count below 20/mm^3, and cryptococcal antigen titre greater than 1024[15].

Other mycoses: Other mycoses documented in HIV/ AIDS include aspergillosis which produce multiple abscesses and rarely granulomas, candidiasis also causing abscesses in brain from haematogenous dissemination from primary focus in respiratory or gastrointestinal tract, and coccidioidomycosis presenting as a basal meningitis causing hydrocephalus or cerebellar or brain stem abscesses. These are however extremely rare and confined to case reports. Even rarer is involvement by *Nocardia asteroides*, *Histoplasma capsulatum* causing meningoencephalitis, zygomycosis, and *Cladosporium bantianum*. Narendra Singh from Manipur reported[26] increased incidence of *Penicillium marneffei* infection among patients with

AIDS next to tuberculosis and *Pneuomocystis carninii* pneumonia. Infection by this fungus is commonly reported from Thailand where it is the third commonest AIDS defining opportunistic infection. In India, other than from Manipur, there are no reports of this mycoses from anywhere else till date.

Protozoal infections

Cerebral toxoplasmosis: Cerebral toxoplasmosis is the most common cause of cerebral mass lesion in patients with AIDS. This is true even in the developing world where tuberculosis is endemic and a frequent cause of such lesions. The disease is eminently treatable, most patients making a full recovery but is fatal if untreated. In USA and Western Europe, nearly 10-30 per cent of HIV seropositive patients die of toxoplasmosis[27], although uncommon, cases of toxoplasma encephalitis (TE) in patients who are seronegative for HIV have also been reported[27].

It is a protozoal parasitic disease prevalent worldwide, its prevalence varying according to dietary preferences in any country. For instance, in certain parts of Europe, particularly France, very high seroprevalence (70-90%) has been observed, attributable to the habit of raw-meat eating, while in the United States it is approximately 30 per cent[28,29]. Little is known about the source of *Toxoplasma gondii* infection for humans in India. Rawal from western India[30] reported almost equal seroprevalence of 37.8 and 37.4 per cent in vegetarians and non-vegetarians. Limited data are available regarding seroprevalence of toxoplasmosis antibodies from India and ranges from 18 per cent in Uttar Pradesh[31] to 57 per cent amongst women of child bearing age and 30 per cent in children in age group of 10-12 yr in Himachal Pradesh, both north Indian states[32].

The coccidian parasite is an obligate intracellular parasite and exists in three forms: the oocyst, tissue cyst or bradyzoite (non replicating organism being responsible for latent disease) and the tachyzoite (replicating form of the organism causing active disease). Development of toxoplasmosis is dependant on host's susceptibility and immune status. Of the two types of immunity, humoral immunity with circulating antibodies is the first to appear and limits extracellular dissemination of the organism. Further protective immunity is mediated by CD8+ cytotoxic T cells that produce interferon-gamma and interleukin-2. The organism can remain quiescent in the host lifelong and clinical infections occur only when an imunosuppressed state leads to parasitic activation.

The majority of the primary cases are asymptomatic. Progressive loss of cellular immunity as in HIV causes reactivation of the dormant lesion in the macrophage system, similar to cryptococcosis which reaches brain by haematogenous spread to cause cerebral toxoplasmosis. Toxoplasmosis develops when CD4 counts fall blow 100 cells/ul.

Predominant neuropathological features of cerebral toxoplasmosis is multifocal necrotizing encephalitis. Localization of multiple lesions with ring enhancement on neuroimaging in basal ganglia, thalamus and fronto-parietal cortex is similar to cryptococcal lesions, and suggests haematogenous spread. The predilection of toxoplasma for the basal ganglia can result in a variety of movement disorders[33]. In contrast to cryptococcal meningitis, the cerebral oedema, encephalitic process and tissue destruction are significant and responsible for majority of neurological morbidity in HIV positive patients presenting with focal brain lesion[34]. Rupture of tissue cysts in AIDS patients results in renewed multiplication of bradyzoites into tachyzoites, which elicits severe inflammatory reaction. Three morphological patterns of lesions are produced based on stage of infection and degree of tissue reaction: (*i*) necrotizing abscesses or encephalitis found in acute stage (less than few weeks duration) seen as poorly circumscribed necrotic foci with variable haemorrhage, perifocal oedema, acute and chronic inflammation admixed with macrophage infiltration, with numerous tachyzoites and encysted bradyzoites along the periphery. Vascular thrombosis/fibrinoid necrosis of vessel wall, with polymorph infiltration, intimal hypertrophy and tachyzoites demonstrable in the hypertrophic arterial wall are common, (*ii*) organizing abscesses are found in cases treated for two weeks or more representing chronic lesions (weeks to months) and are seen as well circumscribed foci of central necrosis with rim of congestion. In contrast to the acute phase, the central foci of acellular necrosis are surrounded by a granulomatous reaction, tightly packed lipid and haemosiderin laden macrophages, prominent hypertrophic occlusive

arteritis with dense lymphocytic cuffing, and only a few organisms, and (*iii*) chronic abscesses are seen in patients treated for a month or more which appear as small cystic cavities or linear orange-yellow scars containing lipid and haemosiderin containing macrophages surrounded by a dense gliotic reaction. Calcification of vessels occurs and organisms are rarely found. In addition to producing mass lesions, CNS toxoplasmosis can present as a diffuse, non necrotizing, rapidly progressive encephalitis histologically seen as nodules of microglial cells with encysted bradyzoites and dispersed tachyzoites within the nodules. This form is unique AIDS patients.

The pathogenesis of necrosis in toxoplasma encephalitis is unclear. A curious feature is the vascular pathology of concentric adventitial thickening and luminal compromise by endothelial cell proliferation in small perforator arteries similar to tuberculous vasculopathy, suggesting a pathogenetic similarity in evolution of the lesions. The 'organizing abscess' lesions of toxoplasma on gross and microscopic feature resemble liquefying tuberculoma and tuberculous abscess causing problems in discrimination, when there is no prior history of AIDS or serological evidence of toxoplasmosis.

CNS toxoplasmosis in autopsy series varies from 4-41 per cent. Most have no evidence of systemic involvement suggesting reactivation of latent infection in CNS. Striking geographic differences are seen in incidence of toxoplasma encephalitis between Europe (17-40.7%), North America (5-14.1%) and Latin America (34.1%)[35]. At our Centre, from 1990 when the first case of HIV was detected, of 113 patients with focal brain lesions who came to autopsy, toxoplasmosis was the single most common aetiological agent (89%), followed by tuberculoma seen in only 7 per cent and primary CNS lymphoma (3.6%) (unpublished data). In a study from Mumbai CNS toxoplasma lesions were seen in 20 per cent of AIDS cases at autopsy[36]. In a clinico-radiological study of 1527 HIV seropositive subjects from Pune, western India[20], toxoplasmosis was the commonest cause of mass lesions (66%). No case of primary CNS lymphoma was recorded[20].

Post HAART era has altered the picture to a variable extent in the West, but no information is available as yet from India, as HAART has been introduced here only recently. No case of adult CNS toxoplasmosis was reported in India prior to the AIDS era, though toxoplasmosis related congenital anomalies and high level of antitoxoplasma antibodies in prenatal mothers has been recognized, especially in northern India[36].

Infection by other protozoans like *Cryptosporidium* and *Plasmodium* does occur in AIDS patients. HIV-1 infection and malaria are common, widespread and overlapping problems in India with HIV being endemic in many parts of the country where malaria is also prevalent making an interaction between them of great public health importance. The association with HIV does not appear to have significantly altered the evolution of the disease. In a limited study of pathology of cerebral malaria, in relation to HIV, the apparently discernable difference was paucity of microglial reaction (Durck granulomas) in white matter, but no significant difference in parasite index (Shankar SK, personal observation).

The association of opportunistic infections by other protozoans (*Acanthmoeba* and *Naegleria*) in AIDS have been reported. *Pneuomocystis carninii* principally involves the lungs, and rarely retina, bone marrow, skin, mastoid and small intestine[37-39]. Till date, only a single case of CNS involvement in a drug abuser is on record[40] who had co-existing *Toxoplasma* and *P. carninii* cysts within cerebral abscesses. At our Centre, we have detected only one case of acanthameba meningoencephalitis[41] .

Bacterial infections

Bacterial infections of the CNS are rare in AIDS patients possibly due to unimpaired neutrophillic response in AIDS. Mycobacterial infections are the most common of the bacterial pathogens that cause CNS involvement in AIDS.

Neurotuberculosis: TBM is the most serious extrapulmonary manifestation of tuberculosis, and co-infection with HIV has probably altered the evolution of the pathological lesion and clinical course. (Most patients with TBM have a CD4 count <200 cells/µl. *Mycobacterium tuberculosis* in association with HIV is common in the developing world and in intravenous (iv) drug abusers. The prevalence of CNS-TB varies

with endemicity of TB in the population. The highest rate in a developed country in autopsy series is 1.4 per cent, among whom 52 per cent were drug users[42]. In developing countries such as India and Africa, it is approximately 12 per cent of unselected autopsies with tuberculoma and tuberculous abscesses occurring in 6 per cent of cases[8,43].

Although Berenguer *et al*[44] from USA noted that nearly 80 per cent of HIV-seropositive cases of TBM were IV drug users, in Indian series, not a single case of IV drug users is on record, and HIV was acquired by heterosexual contact. Even from north-eastern part of India, where IV drug abuse is common, no documented cases of neurotuberculosis with IV drug abuse and HIV are available. At our Institute (unpublished data), among the HIV seropositive cases, 21.9 per cent were alcoholics compared to 5 per cent in HIV negative group. Evidence of pulmonary tuberculosis at the time of hospitalization was evident in 48 per cent of HIV-positive group and 17 per cent in HIV-negative group. Nearly half of the HIV-positive patients developed TBM, while already on antituberculous therapy most often for pulmonary tuberculosis. Generalized lymphadenopathy was found in 34 per cent in HIV-positive group and 14 per cent in HIV-negative group which is similar to western literature[44,45]. Mean CD_{4+} cell count was 196/µl in HIV-seropositive group and 587/µl in seronegative group[46] similar to Western studies[47]. On cranial CT scan evidence of cerebral atrophy was observed in 18.8 per cent of HIV-positive cases and 3 per cent in HIV-negative cases. Focal lesions suggestive of tuberculomas were noted in 8 per cent of HIV-seronegative group and 3 per cent of seropositive group from Bangalore (unpublished data), compared to higher frequency (15-24%) of tuberculomas associated with TBM in HIV positive cases from West[44,48]. Spinal epidural tuberculosis appears to be relatively less frequent in India, when compared to cranial tuberculosis, though this impression needs to be further substantiated with actual data.

In reports from the West wherein TBM is rarely encountered, the macro- and microscopic features of TBM in HIV-seropositive cases are reported to be no different from HIV-negative cases. In contrast, in reports from Western India, distinct differences were noted between TBM in seropositive and seronegative cases[49] with the basal exudates in HIV-positive cases being serous and relatively inconspicuous, but yet teeming with acid-fast organisms in the smear made from basal exudates. Without prior knowledge of HIV seropositive status, some of the brains in gross examination can be labelled 'normal'. It is difficult to label these as cases of primary infection of meninges, as they had pre-existing pulmonary lesions. Even at our Institute, from south India, similar features were noted, though occasional cases in HIV-positive group had thick basal exudates (unpublished data). This could reflect slow evolution of meningitic process or acute exacerbation of pre-existing pathology following immunosuppression and fall in CD_4 cell count. Tuberculous arteritis, phlebitis, abscess formation, cerebral and brainstem infarcts were more frequent in HIV-positive cases similar to the study from Mumbai[49]. Whether these phenotypic differences in pathology of TBM in West versus East is secondary to differences in CD4 counts, immune status or the HIV-1 clade C subtype needs to be probed. In many of the studies from India, serial CD_4 cell count and viral load is not available due to technical reasons and this forms a limitation in understanding the evolution of the disease.

Viral infections

Viral infections are frequent complications of AIDS. The CNS is mainly involved by two groups of viruses: the herpes family [primarily cytomegalovirus (CMV) and less frequently varicella zoster (VZV) and herpes simplex virus (HSV)] and papova virus.

Cytomegalovirus belongs to the Herpes family and has been identified as a ubiquitous pathogen in several mammals. The infection predominates in people living in underprivileged countries and densely populated areas[50] and sexually promiscuous homosexuals[51]. It is known to cause encephalitis, ventriculo-encephalitis, polyradiculitis, radiculomyelitis and peripheral neuropathies. CMV infection of the brain has been documented in approximately 30 per cent of patients with AIDS[5], though CMV encephalitis is a rare clinical diagnosis in patients with HIV[52]. It occurs in patients with very low CD4 counts of <50 cells/µl. Two distinct clinical and neuropathological entities of CMV encephalitis has been recognized[53,54]. The first is, encephalitis with dementia, revealing microglial nodules in the grey

matter of the cortex, basal ganglia and brain stem. The second form is ventriculo-encephalitis, with necrosis and leucomalacia in the periventricular zones. From India no serological or pathological data are available regarding the prevalence and pathological spectrum. From NIMHANS, only one case of CMV ventriculoencephalitis associated with HIV is recorded during the past ten years[41].

Although there is a strong association between immunosuppression and herpes zoster, only a few patients with AIDS develop neurological complications associated with VZV. Patterns of VZV involvement of CNS in AIDS include (*i*) multifocal leukoencephalitis with and without an inflammatory vasculopathy[55,56] in which multiple partly demyelinating lesions surrounded by inclusion-bearing oligodendrocytes are seen in deep white matter suggesting haematogenous spread of infection; (*ii*) bulbar encephalitis or transverse myelitis secondary to transsynaptic spread to brain or spinal cord from VZV ophthalmicus, trigeminal, dermatomal or myotomal infection; (*iii*) ependymitis/ventriculitis mimicking CMV infection; and (*iv*) leptomeningeal vasculitis or vasculopathy often associated with haemorrhagic infarcts in brain or spinal cord. Large arteries involved may show granulomatous vasculitis, or vascular necrosis and thrombosis with little or no inflammation. One case of vertebrobasilar thrombosis causing infarcts in posterior circulation associated with VZV infection was recorded at NIMHANS. Another case of multifocal leukoencephalitis caused by VZV was seen at autopsy in an AIDS patient who succumbed to cerebral malaria (unpublished data).

Eosinophillic intranuclear inclusions of Cowdry type A are found in oligodendrocyte, astrocytes, occasional neurons, ependymal cells, endothelial cells, and schwann cells. VZV infection can be confirmed by immunocytochemical/*in situ* hybridization techniques. Polymerase chain reaction (PCR) for detecting VZV DNA in CSF has also been found useful in early diagnosis of VZV associated neurological disease.

HSV encephalitis does not seem to occur more frequently in AIDS than in immunocompetent individuals. Atypical forms of HSV encephalitis are reported in patients with AIDS with non-necrotizing encephalitis occurring at sites other than temporal or frontal lobes, usually involving brain stem and more slowly progressive than classical HSV encephalitis with persistence of viral antigen and DNA[57]. A single case of HSV encephalitis was observed at our centre with no discernible haemorrhagic/necrotizing lesions seen but viral antigen was demonstrable by immunochemistry[41].

Progressive multifocal encephalopathy (PML) is a fatal, demyelinating disease caused by JC virus in immunocompromised individuals. Though once considered relatively uncommon, PML is now diagnosed more frequently, mainly due to the association with AIDS, greater awareness among neurologists and fairly diagnostic imaging characteristics. Though no definite therapy is available, introduction of HAART has significantly altered the course of the disease, enhancing the survival period.

The causative agent, Polyoma virus is considered to be ubiquitous, the infection usually acquired during childhood, by sewage contamination similar to poliomyelitis. Serological studies have suggested that 70-90 per cent of adults have been infected[58]. The primary infection has not been associated with clinical symptoms, the virus remaining latent in kidney, brain, and peripheral blood lymphocytes[59,60]. The means of JC virus transmission is still speculative with most frequent postulate being respiratory spread. The prevalence of PML in patients of AIDS has ranged from 1 to 10 per cent and has been reported as an AIDS defining illness in 57 per cent of patients presenting with PML[61].

JC virus essentially infects oligodendroglia and astrocytes and the hallmark is multifocality of the lesions. Nearly all cases of PML involve the cerebral white matter, but it may also involve white matter of cerebellum, brainstem and spinal cord. Histology reveals basophilic intranuclear inclusions in oligodendroglia, reactive astrocytosis with 'tumour like' bizarre nuclei in the demyelinating zones. The lesions characteristically involve subcortical white matter, extending to the lower layers of the cortical ribbon. By immunocytochemistry JC viral antigen can be demonstrated both in the oligodendroglial nuclei and astrocytic cytoplasm, extending along the processes. In view of its multifocal nature of pathology, PML needs to be considered as a differential diagnosis

in dealing with focal brain lesions. Ammassari *et al*[34] in a series of 281 focal brain lesions, associated with HIV, reported PML in 18.2 per cent of cases, toxoplasma encephalitis and primary CNS lymphoma preceding it. In India, with the advent of the HIV era, neurologists, based on neuroimaging started making a diagnosis of PML, though most are not confirmed by histology or molecular biological techniques. Recently, JCV was shown to infect cerebellar neurons resulting in cerebellar degeneration in some HIV infected patients[62]. Prior to 2000, at NIMHANS, not a single case of PML was diagnosed. Subsequently in 2 yr (2001-2002), histologically and immunohistochemically confirmed cases of PML were recognized in four steriotactic biopsies and five autopsies[63]. Similarly from western India also based on clinical and neuroimaging characteristics, cases of PML, associated with HIV were diagnosed[20]. Significant genomic diversity in JCV has been identified, majority of strains in India and Africa being essentially similar[64]. The prevalence of PML in India and Africa is possibly related to altered modulatory role of HIV-1 subtype C, in contrast to HIV-1 B in Europe and USA. A sequence diversity in the regulatory region and nuclear localization region of Tat amongst HIV-1 clade B and C has been recognized[65]. JCV contains sequences in the 5' end of late RNA species with extensive homology to HIV-1 TAR (transactivation response element), thus facilitating Tat activation of JCV promoter. HIV-1 Tat protein can induce regulatory proteins like nuclear factor Kappa B (NF-KB), NF-1 in microglial cells which in turn can activate JCV, lying dormant in oligodendroglia or astrocytes[66,67].

The HIV and JCV interaction can be strain dependent. HIV infection induces a wide variety of cytokines, chemokines and adhesion molecules in the brain[68,69] and several chemokine receptors in astrocytes[70]. These increased expression of inflammatory mediators, along with Tat induced monocyte chemoattractant protein (MCP-1) expression in astrocytes facilitate the migration of monocytes and lymphocytes into the brain, a pathogenetic mechanism for HIV associated dementia. JCV associated dementia could also be mediated by similar pathway, synergistically commanding HIV associated cognitive deficits. HHV-6, another benign oligodendrotropic beta-herpes virus

is found to be closely associated with JCV[71,72]. The differential transactivation potential of various HIV-1 subtypes on these viruses needs to be explored. High prevalence of PML in white males in contrast to African American males suggest racial/genetic differences[73]. Whether similar phenomenon is responsible for low prevalence of PML in India and sub-Saharan Africa needs further probing.

CNS neoplasms

In the western literature, the incidence of primary central nervous system lymphoma (PCNSL) in HIV infected population is documented to be on the rise. In HIV infected adult patients, the incidence of this neoplasm is 1000-3000 times more common[74] occurring in 2-5 per cent of patients with AIDS[75]. PCNSL associated with HIV-1 infection is virtually multifocal[76] and Epstein-Barr virus is almost always found in the tumour[77]. Despite marked increase in the number of AIDS cases in India and other Asian countries, very few cases of HIV associated neoplasia are recognized. During the past 10 yr in Bangalore, south India among 29 cases of PCNSL tested for HIV, three were positive. From north India among 80 cases of PCNSL, not a single case was positive for HIV[78]. In Australia, the cumulative incidence of non-Hodgkin's lymphoma (NHL) among AIDS patients is 10 per cent, one-fifth of them having primary CNS lymphomas, manifesting with advanced immunosuppression[79]. Recent studies recorded malignant lymphomas in biopsy/necropsy specimens in 4 per cent from Northern Thailand, 4.3 per cent from Papua New Guinea and 5.6 per cent from Japan and 2.3 per cent from Indonesia[80]. It is possible that in developing Asian countries, lymphoma-related lymphadenopathy may have been diagnosed as infective lymphadenitis, because of high prevalence of infections and clinical bias.

Kaposi's sarcoma, a vascular neoplastic lesion that has come to scrutiny following the association between homosexuality and HIV infection, rarely involves nervous system, that too as a metastasis from extracranial site. Till date, only one case of cutaneous Kaposi sarcoma, without CNS metastasis in a heterosexual male has been reported from India[8]. Whether it is related to low prevalence of HHV-8 infection in Indian population needs to be studied.

HIV-specific nervous system changes

In contrast to secondary injury to the brain following HIV associated opportunistic infections, widespread CNS injury is caused by HIV *per se*, referred to as primary pathology. This primary pathology includes a range of inflammatory disorders as well as neuronal loss along with dendritic damage and synaptic loss. During the early asymptomatic phase, non specific changes like astrocytosis, perivascular lymphocytic cuffing, diffuse and variable degree of microglial proliferation are described[81]. At this stage neuronal loss is not a feature[82]. This is a stark contrast to significant frontal lobe neuronal loss of 38 per cent in symptomatic HIV cases[83]. The HIV specific pathology manifests in different phenotypic forms, during the course of illness. This manifestation appears to be controlled by trafficking of HIV virus, within infected immune cells and as free virus from the peripheral blood to the central nervous system crossing the blood brain barrier. The process is complex and dynamic involving many cell types (like microglia/macrophages, astrocytes, vascular endothelial cells and rarely neurons), cell surface receptors ($CXCR_4$, CCR_5), the turn over kinetics and migratory capacity of the cells[84]. Principal sites of productive HIV infection of CNS are microglia/macrophages, facilitated by surface receptors[85]. In the study from the West, the macrophages are found to show shift of $CXCR_4$ receptor to CCR_5 during the course of disease, correlating with the formation of HIV-associated multinucleated giant cells. This receptor shift has been described to be lacking in the Indian HIV strains probably modifying the course of the disease[86].

HIV encephalitis: HIV encephalitis occurs in 15-40 per cent of cases with AIDS[87], microscopically characterized by multiple foci of inflammatory cells, including macrophages, microglia and multinucleated giant cells. The multinucleated giant cells are the histological hallmark of HIV encephalitis, harbouring the virus. The prevalence of HIV encephalitis and presence of multinucleated giant cells are considered to be uncommon in India, though no systematic studies are available.

HIV encephalopathy, characterized by diffuse, symmetric white matter demyelination, astrocytosis and presence of microglia and multinucleated giant cells could be a part of spectrum of HIV specific brain pathology, overlapping with HIV encephalitis[83]. Curiously in the autopsy material from south India, multiple foci of demyelination in the white matter was noted in cases of HIV associated cryptococcal and toxoplasma infections, especially close to vessels. It is not clear if this feature is a reflection of HIV leucoencephalopathy or related to vasculopathy associated with opportunistic infections. Whenever ring enhancing lesions are observed on imaging, empirically antitoxoplasma drug regimen is initiated. In some of the autopsied cases of toxoplasma encephalitis and cryptococcal meningitis multiple burnt out scars are seen. Similarly in the brains with these two opportunistic infections large zones of demyelination are seen similar to HIV leucoencephalitis. How these white matter lesions contribute to the cognitive dysfunction is not clear.

Vacuolar leucocephalopathy is occasionally found in some of these cases. Similarly demyelination of the posterior columns of the spinal cord was observed in nearly half of the autopsied cases, while vacuolar myelopathy was rare. However, none of the cases had neurological deficits of myelopathy (S.K. Shankar, unpublished data)..

HIV encephalitis is known to be accompanied by depletion of specific population of neurons in neocortex, limbic system and basal ganglia. The selective damage to neuronal population in the frontal cortex[88] in association with dendritic abnormalities may be the pathological basis for frontal lobe neuropsychometric abnormalities and HIV associated dementia. The mechanisms of neurotoxicity are considered to involve vulnerability of specific neuronal population to viral proteins, cytokines secreted by activated macrophage/microglial population altered calcium binding proteins and activation of glutamate receptors in the neurons[89,90]. HIV-1 proteins gp120 and Tat block the response of cells to growth factors, platelet derived growth factor (PDGF)[91] and nerve growth factor (NGF)[92]. In addition, Tat may be directly toxic to neurons[93], may activate glial cells to release cytokines[94] or alter release of fibroblast growth factor-1 (FGF-1) causing deleterious effect on survival of neuronal populations[95].

The prevalence of HIV associated dementia (HAD) among otherwise asymptomatic subjects is estimated to be 15-30 per cent in USA and Europe[96,97]. In contrast, an unusually low incidence of HAD has been reported in India[98,20]. Usually low prevalence of HAD in underdeveloped and developing countries have been attributed to underdiagnosis, short life expectancy and short survival following HIV infection associated with opportunistic infections. However from a tertiary care neurological centre, six cases of HAD were found among 427 HIV-infected individuals, suggesting that it may not be an artifact (unpublished data). However, it is important to point out that psychometry was not carried out routinely in all the cases, thus necessitating further prospective systematic studies. In an attempt to identify the viral determinants for this low prevalence of HAD in India caused by HIV-1 clade C in contrast to HIV-1 clade B associated high prevalence in the West, variation in Tat protein sequence and its influence on monocyte chemotaxis were studied[99]. Conservation of cystine at position 31 in non-subtype C viruses (CC) was observed, while in subtype C, it was replaced by serine (CS). The 'CS' variant was found to be defective for monocyte chemotactic activity without loss of transactivation property, while both functions were preserved in non-C HIV-1 subtypes. Though the evidence is not conclusive, this could be one of the factors for the low incidence of HIV-1 encephalitis and HAD in Indian subcontinent.

Till date, no neuropathological data are available in literature related to HIV encephalitis and HAD in HIV-1 clade C infected individuals. During the initial phases of HIV/AIDS, the opportunistic infections due to immunocompromised state took the centre stage, accounting for the high mortality. Slowly specific HIV induced neuropathology, never seen prior to the AIDS epidemic and found only in HIV-infected individuals without evidence of another cause was recognized[100]. Productive infection of the CNS by HIV, monocyte/macrophage/microglial cells taking the active role and astrocytes a passive role in pathogenesis has been demonstrated by various virological and morphological techniques. Pathological basis of HIV dementia still remains a subject of debate, while HIV leukoencephalopathy, HIV encephalitis and diffuse poliodystrophy have been well characterized[101]. It seems likely that HIV dementia represents a specific neuronal dysfunction resulting from the compounding effect of several mechanisms, some of them being reversible.

Neuropathology of paediatric AIDS

Neurological manifestations in paediatric cases are commonly secondary to immunodeficiency or direct effect of HIV on the nervous system[102]. Cerebrovascular diseases and lymphomas are most common, and CNS lymphomas are mostly associated with Epstein Barr virus (EBV) infection. Opportunistic CNS infections are uncommon, with monilial and cytomegaloviral infection being the common ones. Unlike adults, cerebral toxoplasmosis is rare in children and haemophiliacs. Direct effects of HIV-1 on CNS in children manifest as microcephaly, diffuse gliosis, basal ganglia mineralization and HIV encephalitis. HIV related encephalopathy affects >50 per cent of children with AIDS[103] with characteristic multinucleated giant cells. Progressive encephalopathy in HIV-1 with its classical triad of microcephaly with brain atrophy, delayed developmental milestones and progressive motor dysfunction should be discriminated from metabolic disorders with progressive cerebral degeneration in developing countries. Certain neuropathological features are unique to paediatric HIV infection/AIDS. Mineralization of small penetrating vessels in basal ganglia are the most common findings seen in more than 90 per cent of cases at autopsy[104]. Its pathogenesis is unknown but believed to be related to transient alteration in blood- brain barrier. Other vascular changes unique to paediatric AIDS include inflammation of intraparenchymal vessels resembling a vasculitis, intimal thickening of larger leptomeningeal vessels and occasionally a granulomatous vasculitis causing infarcts in brain.

The paediatric CNS appears to be unusually susceptible to even low levels of HIV-1 infection. No neuropathological studies on paediatric AIDS are available from India. At our Centre, we have seen one case each of cryptococcal meningitis and toxoplasma encephalitis in two children who succumbed to AIDS (unpublished data).

Highly active antietroviral therapy (HAART tri- or multi-therapies)

HAART has dramatically improved the course and prognosis of HIV disease in many of the developed

countries where this treatment is widely available. Though the most dramatic benefit of HAART restored functional immune system affording protection against opportunistic infections, improved neuropsychological performance, its effect on cognitive disorders/dementia is less satisfactory[105,106]. The antiretroviral treatment is found to reduce viral load and enhance circulating T lymphocyte counts. But viral mutations leading to viral resistance, side effects of the drug and lack of compliance to therapy, especially in developing countries remain major problems. The restored immune function has reduced the effect of opportunistic infection. In India, antiretroviral therapy has been initiated around 1998 depending on the availability and affordability of the drugs.

Post-HAART era

In the West because of significant improvement in control of opportunistic infections and longer survival of the patients, autopsies on AIDS cases have decreased dramatically, resulting in non-systematic studies[107-109]. There was an overall decrease of cerebral toxoplasmosis, cytomegalovirus encephalitis and HIV encephalitis, while the incidence of PML and malignant non Hodgkin lymphoma (NHL) has remained unchanged, though survival period is enhanced. Severe leukoencephalopathy with intense perivascular lymphocytic and histiocytic infiltration is described following HAART, probably as a response to immune reconstitution[110].

In India, antiretroviral therapy was initiated in 1996, in a limited scale, both to adults and antenatal mother to prevent mother-to-child transmission. No neuropathological observation from the brains of patients who received antiretroviral therapy is available from India to compare with West, though clinically follow up for maximum period of four to five years is available. Clinicians consider immune reconstitution syndrome whenever the patient on antiretroviral therapy deteriorates after initial response. Unfortunately, in many of these cases sequential CD_4/CD_8 counts and viral load are not available for objective evaluation. In near future with the availability of facilities, the management and follow up strategies are expected to improve for systematic analysis.

Neuromuscular disorders in HIV/AIDS

The demonstration of direct involvement of the CNS by HIV led many workers to seek a similar role for the virus in the peripheral nervous system. In fact, peripheral neuropathies were among the first neurological conditions to be described in AIDS[2], and is the most frequent complication of HIV infection. The reported incidence varies in different series from 15 to 50 per cent[111]. However, subclinical evidence based on electrophysiologic studies has been reported in 50 to 90 per cent of patients with AIDS[112] while autopsy studies demonstrate pathological abnormalities of the nervous system in general in over 95 per cent of patients dying of AIDS[6,113]. With the introduction of HAART although CNS involvement by opportunistic infections and HIV associated dementia have declined significantly, incidence of peripheral neuropathies is actually increasing owing largely to the neurotoxic effect of antiretroviral drugs.

Classifications of HIV related peripheral neuropathies have subsequently been evolved based on the different clinical syndromes that occur at different stages of HIV infection. During early stages of HIV infection when there is no immunosuppression, patients are more susceptible to immunological disorders. In the later stages when immunosuppression supervenes, opportunistic infections and tumours cause various peripheral nerve syndromes. Additionally, peripheral neuropathies can also result from neurotoxic effects of drugs or malnutrition.

The clinical presentations can encompass the entire spectrum of peripheral nerve disorders. The spectrum of neuropathies described include inflammatory demyelinating neuropathy (IDP), distal symmetric sensory polyneuropathy (DSPN) which is often painful, progressive polyradiculopathy, mononeuritis and mononeuritis multiplex and autonomic neuropathy. The manifestation of neuropathy is related to the stage of the disease with the inflammatory demyelinating neuropathies occurring early at the time of seroconversion, followed by DSPN, polyradiculitis and autonomic neuropathy at the time of full blown AIDS. Mononeuritis multiplex can occur at any stage of the disease secondary to vasculitis, cytomegaloviral infection, lymphoma or cryoglobulinaemia.

Peripheral nerve syndromes reported to occur at the time of seroconversion include acute inflammatory polyradiculopathy (AIDP)[114,115], lower motor neuron facial palsy often associated with aseptic meningitis[115] and bilateral brachial neuritis[116]. All these syndromes are self limiting and no neuropathological studies are available. These could be evidence of early neurotropism of the HIV virus as it has been isolated from CSF in some cases[114,115]. Both acute (AIDP) and chronic inflammatory demyelinating polyradiculopathy (CIDP) have been described to occur in HIV seropositive cases[117-120]. Except for the presence of CSF pleocytosis (up to 300 cells/mm^3 in AIDP and up to 50 cells/mm^3 in CIDP) the clinical manifestations, course and response to treatment are identical to that seen in HIV seronegative individuals[117]. The pathogenesis too may be similar as circulating autoantibodies reactive with peripheral nerve components have been reported[121,122] and the patients respond to different modes of immunomodulation such as plasmapheresis, corticosteroids and intravenous immunoglobulins.

Neuropathological studies are limited to sural or superficial peroneal nerves[117-120], which show variable inflammation, subperineurial oedema, de/remyelination best seen on teased fibre studies and axonal degeneration. Cornblath et al[117] demonstrated by immunohistochemistry that most of the inflammatory infiltrate that surround endo/epineurial vessels (<80 µm) are T cells. Attempts to localize the HIV virus in the nerves by in situ hybridization have been uniformly unsuccessful but immune deposits have been seen in nerve biopsies. The virus was cultured from one nerve but its significance is unclear as it could be a circulating macrophage containing the virus[9,117]. This makes a direct role for HIV in the pathogenesis for AIDP or CIDP unlikely. Inflammatory demyelinating neuropathies (IDP) can also occur later on at the stage of AIDS related complex (ARC) and AIDS. IDP when associated with low CD4 counts is usually secondary to CMV infection[123].

Vasculitic neuropathy: Of the various peripheral nerve syndromes in HIV/AIDS, vasculitis of the peripheral nerve occurs in up to 3 per cent of patients with ARC or full blown AIDS[124]. In HIV/AIDS, vasculitis of the peripheral nerve may be the first sign of HIV infection. Its occurrence has been noted even in asymptomatic seropositive patients[118]. In most patients the vasculitis is not systemic. Pathologically, there is marked involvement of the microcirculation with inflammation and fibrinoid necrosis of arteries smaller than those that are typically affected in polyarteritis nodosa. Inflammatory cells have been immunologically characterized as CD8+ T cells and macrophages. Le Faucheur et al[125] studying 100 patients with HIV associated peripheral neuropathy found that the CD4 counts in patients with mononeuritis multiplex (125 cells/µl) were lower than those with IDP (194 cells/µl) and higher than patients with DSPN (108 cells/µl in mild and 66 cells/µl in severe form of the disease).

Vasculitis associated with CMV is seen in the later stages of HIV infection and is distinct both clinically and histopathologically by its rapid progression and involvement of endoneurial vessels, in the form of necrotizing vasculitis with polymorph infiltration. The CD4 counts are usually less than 50/µl. CMV inclusions have been seen in the endothelial as well as inflammatory cells. CMV antigen was not demonstrable by immuno-histochemistry in any of the cases studied at our Centre.

The pathogenesis of vasculitis in HIV infection is largely speculative. The finding of immunoglobulin deposits, complement as well as immune complexes on the vessel wall in some studies suggests an immune mediated disorder[126-128]. Circulating immune complexes directed against the HIV virus itself or induced by the opportunistic infections are commonly observed in patients with AIDS. These complexes if deposited on vascular walls could conceivably initiate vascular injury as in polyarteritis nodosa. A direct role by viral invasion of the peripheral nerve was also considered following isolation of the virus from peripheral nerve homogenates[9,129,130]. But the viral antigens have never been detected in the peripheral nerve either by PCR[131] or by immunohistochemistry even in the nerve from which the virus was isolated[129,132,133]. Gherardi et al[134] reported evidence of HIV viral replication in perivascular macrophages in two patients with nacrotizing vasculitis and AIDS by in situ hybridization.

The other forms of peripheral nerve involvement in HIV infection include DSPN which is the most common form of peripheral neuropathy in AIDS. While clinical and electrophysiological abnormalities are detected in up to 35 per cent of patients[135], pathological changes have been found in all patients dying of AIDS[136]. Histologically, most workers describe axonal loss with little inflammation. Simpson & Wolfe[137] studying 165 cases noted that the frequency of DSPN varied inversely with CD4 counts below 200/µl. Rance *et al*[138] demonstrated degeneration of the gracile tract in the spinal cord and proposed that DSPN is a dying back neuropathy secondary to ganglionitis/gracile tract degeneration. A direct effect by the virus was also considered following isolation of the virus from the peripheral nerve in a single case[9] and demonstration of virus like particles in the axoplasm of the nerve fibre in another case[139] by electron microscopy. Vital *et al*[140] reported HIV viral replication in perivascular macrophages in two patients with DSPN suggesting that these could be local sites for replication of the virus. Other factors implicated include the neurotoxic effects of circulating gp120, local release of tumour necrosis factor α and other T-cell and macrophage related cytokines. In fact, tumour necrosis factor α is known to enhance HIV replication *in vitro* and also cause tissue damage in peripheral nerve[141]. The pathogenesis of vasculitis in HIV/AIDS is therefore possibly a complex interaction between immune complexes, cytokines that induce the macrophages to enhance HIV replication and initiate the pathway of vascular injury resulting in vasculitis.

An uncommon form of HIV associated neuropathy that is treatable (with zidovidine and corticosteroids) and enters the differential diagnosis of DSPN is the diffuse infiltrative lymphocytosis syndrome (DILS). It is a multisystem disorder that mimics Sjogren's syndrome. Peripheral nerve manifestations include a painful, sensorimotor axonal neuropathy[142]. Nerve biopsies show characteristic angiocentric infiltrates of CD8 cells without necrotizing arteritis. Interestingly, the HIV proviral load in whole nerve extracts in DILS are more than 100,000 fold higher than that in other HIV associated neuropathies. In contrast, the viral load in plasma is low, suggesting local viral replication. Gherardi *et al*[143] by PCR techniques demonstrated that the CD8 cells are polyclonal and hence not lymphomatous.

Toxic neuropathies: Nucleoside analogues Zalcitabine (ddC) and Didanosine (ddI) and Stavudine (d4T) have been shown to cause a dose-dependant neuropathy. Zidovidine also a nucleoside analogue causes a myopathy but not a neuropathy.

At NIMHANS, Bangalore, we have studied 15 cases of peripheral neuropathy as the presenting manifestation of HIV. CIDP was seen in five, which included multifocal motor neuropathy with conduction blocks in one case. Vasculitic neuropathy with necrotizing large vessels vasculitis indistinguishable from collagen vascular disease was seen in four[144]. Three presented with painful distal symmetric polyneuropathy without evidence of CMV infection. Two of these cases had received antiretroviral therapy. By electron microscopy, virus–like particles were demonstrable within the schwann cell cytoplasm and perivascular macrophages in one case of necrotizing vasculitis. However, immuno-histochemically HIV antigen was not detectable probably due to the low viral density and antigen load, which is in keeping with most studies in literature. Diffuse infiltrative lymphocytosis syndrome has not been described from India. Wadia *et al*[20] from Pune reported 128 cases of peripheral neuropathies associated with HIV wherein herpes zoster (63 cases) and predominantly sensory neuropathies (51 cases) were the commonest forms.

Subclinical involvement of the peripheral as well as central nervous system is being increasingly documented by electrophysiological studies. At our Institute, 20 asymptomatic HIV seropositive subjects were evaluated with Mini Mental Status Examination (MMSE), EEG, nerve conduction and multimodality evoked potential studies[145]. Four subjects had MMSE score of less than 23 suggesting cognitive impairment though they were functioning normally. EEG was mildly abnormal in eight cases. Brain stem auditory evoked potentials (BAER) studies showed peripheral auditory pathway involvement in 23.5 per cent of subjects. Somatosensory evoked potentials (SSEP) was abnormal in two with delay in N20 latency. Nerve conduction studies showed significantly decreased mean nerve conduction velocity (NCV) in median and sural nerves compared to controls. Hence long term follow-up studies are essential to understand significance of these studies.

Electrophysiological studies have also demonstrated abnormalities in visual pathway even in the absence of visual symptoms. From autopsy studies at our Institute[146] the pathological changes in the optic nerves were studied in the subclinical cases. Axonal pathology was the cardinal finding in addition to demyelination that corresponded to the prolonged P100 latencies in the visual evoked potentials recorded antemortem in these patients. Additionally, cryptococcal parenchymal infiltration causing sectoral destruction of optic nerve was also found not commensurate with the degree of electrophysiological abnormality[146].

Myopathies: Myopathy is a well recognized complication of AIDS and can occur in three main forms; polymyositis, nemaline rod myopathy, and zidovidine induced myopathy. Polymyositis is the most common of the AIDS-associated myositis, and maybe the presenting sign of HIV infection[147]. Inflammatory cell infiltrates of lymphocytes, macrophages, atypical histiocytes, and occasionally multinucleated giant cells are reported. HIV virus has not been identified in the myofibres but presence of viral antigens within infiltrating CD4 cells was shown by immunohistochemistry though *in situ* hybridization studies were negative[147].

The pathological features of the nemaline rod myopathy occurring in patients with HIV infection are identical to the adult onset nemaline myopathy[111,148].

Zidovidine used in the treatment of AIDS can cause myalgia in up to 8 per cent of patients[139] which resolves on discontinuation of the drug. Muscle biopsies show ragged red fibres indicative of mitochondrial damage, which disappear on discontinuing the drug. Though clinicians do see cases of myopathy and myositis associated with HIV/AIDS, no systematic studies are available from India.

At NIMHANS, Bangalore, one case of amyotrophic lateral sclerosis (ALS) - like disorder with HIV clade-C was detected[150]. ALS-like disorder in HIV is extremely rare, with only seven cases being recorded in literature. Its importance lies in the reversibility of the disorder following antiretroviral therapy[151]. The cause for anterior horn cell dysfunction remains unknown. As the HIV virus has not been known to directly infect neuronal cells[152], it is speculated that damage to anterior horn cells could be due to glutamate mediated excitotoxicity, or direct neurotoxic effect of gp120 and Tat protein of HIV. Immune mediated mechanisms has also been suggested following detection of anti-asialo GM1 antibody in ALS-like disease associated with HIV[153].

The neuromuscular junction has been considered to be spared by the HIV virus. However at our Centre, three cases of myasthenia gravis like syndrome associated with HIV are noted. Sporadic reports of this association have also been reported in Western literature.

Conclusions

The spectrum of HIV associated complications reported from India - south India (Bangalore), western India (Mumbai and Pune) appears to be different from the West. The differences could relate to variations in HIV clade subtype. Large, systematic autopsy studies correlating with clinical aspects need to be documented for comparison with Western data. Unfortunately autopsy studies are dwindling due to phobia on part of pathologists to carry out autopsies on HIV cases. With the National policy of providing antiretroviral therapy to antenatal mothers and adult patients with HIV/AIDS, a new cohort of patients is emerging with altered biology of infection confusing the clinical picture. With passage of time, these patients need to be evaluated in the light of new knowledge emerging following specific therapy and compare with the cohort which did not receive antiretroviral therapy. An intermediate cohort of patients who received the HAART for sometime and discontinued the therapy needs to be evaluated separately.

The following are the researchable issues necessary to understand the biology of neuroAIDS in India with its unique spectrum of opportunistic infections, and difference in clade subtype: (*i*) The spectrum of opportunistic infections and their pathomorphological features modulated by multiple infections in association with clade subtype C; (*ii*) Pathology of HIV/AIDS in paediatric age group to correlate with cognitive dysfunction/scholastic performance in long term survivors; (*iii*) Spectrum of neuropathological lesions in IV drug abusers in India with special emphasis on the influence of HIV subtype/recombinant strains on the evolution; (*iv*) Neuropathology of HIV associated

cognitive dysfunction/dementia; (*v*) Neuropathology of HIV encephalitis/encephalopathy with special emphasis on viral load and macrophage function; (*vi*) Alteration in pathobiology of HIV related complications with immune reconstitution induced by treating opportunistic infections even without HAART; (*vii*) Neuropathology of HIV/AIDS in the heralding era of HAART therapy in India; (*viii*) Role of host genetic factors in susceptibility to neurological manifestations of HIV infection; and (*ix*) The effect of antiretroviral therapy in antenatal mothers and their influence on evolution of pathological lesions in paediatric AIDS especially HIV encephalopathy/HIV encephalitis.

Acknowledgment

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