Research article

Nonopportunistic Neurologic Manifestations of the Human Immunodeficiency Virus: An Indian Study
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Abstract

Context: HIV-1 is a neurotropic virus. In a resource-limited country such as India, large populations of affected patients now have access to adequate chemoprophylaxis for opportunistic infections (OIs), allowing them to live longer. Unfortunately the poor availability of highly active antiretroviral therapy (HAART) has allowed viral replication to proceed unchecked. This has resulted in an increase in the debilitating neurologic manifestations directly mediated by the virus.

Objective: The main objective of this study was to identify and describe in detail the direct neurologic manifestations of HIV-1 in antiretroviral treatment (ART)-naive, HIV-infected patients (excluding the neurologic manifestations produced by opportunistic pathogens).

Design: Three hundred successive cases of HIV-1 infected, ART-naive patients with neurologic manifestations were studied over a 3-year period. Each case was studied in detail to identify and then exclude manifestations due to opportunistic pathogens. The remaining cases were then analyzed specially in regard to their occurrence and the degree of immune suppression (CD4+ cell counts).

Setting and Patients: The study was carried out in an apex, tertiary, referral care center for HIV/AIDS in India. All patients were admitted for a detailed analysis.

No interventions were carried out, as this was an observational study.

Results: Of the 300 cases, 67 (22.3%) had neurologic manifestations due to the direct effects of HIV-1. The HIV infection involved the neuroaxis at all levels. The distribution of cases showed that the region most commonly involved was the brain (50.7%). The manifestations included stroke syndromes (29.8%), demyelinating illnesses (5.9%), AIDS dementia complex (5.9%), and venous sinus thrombosis (4.4%). The other manifestations seen were peripheral neuropathies (35.8% of cases), spinal cord pathologies (5.9% of cases), radiculopathies (4.4% of cases), and a single case of myopathy. The onset of occurrence of these diseases and their progression were then correlated with the CD4+ cell counts.

Conclusion: HIV infection is responsible for a large number of nonopportunistic neurologic manifestations that occur across a large immune spectrum. During the early course of the disease, the polyclonal hypergammaglobulinemia induced by the virus results in demyelinating diseases of the central- and peripheral nervous systems (CNS and PNS). As the HIV infection progresses, the direct toxic effects of the virus unfold, directly damaging the CNS and PNS, resulting in protean clinical manifestations.

Introduction

HIV-1 is known to demonstrate a strong tropism for the neurologic tissues right from the initial stages of infection. The microglial cells in fact form one of the early and most important reservoirs for this virus, where it lies dormant until activated. With the advent of antiretroviral drugs and effective chemoprophylaxis for OIs, the life span for patients infected with HIV has increased considerably. In a resource-limited country such as India, where antiretroviral drugs are not yet affordable for large sections of the population, cheap and effective chemoprophylaxis for OIs has significantly reduced morbidity and increased longevity. All this has resulted in the observance of a large number of clinical neurologic manifestations, which are not due to OIs.

Neurologic manifestations occur over the entire spectrum of HIV disease. During seroconversion aseptic meningitis, Bell's palsy and acute encephalopathy can be seen. With early immunodeficiency there is a polyclonal hypergammaglobulinemia resulting in a large number of demyelinating and inflammatory disorders, such as CNS demyelination, demyelinating and axonal forms of the Guillain-Barré syndrome, polyneuritis cranialis, and polymyositis. With advanced immune suppression the direct toxic effects of the virus come into play, predominantly due to excessive and inappropriate elaboration of cytokines, producing manifestations such as AIDS dementia complex, distal painful sensory neuropathies, and vacuolar myelopathies.

A study of the various nonopportunistic neurologic manifestations that can be seen due to HIV infection and their association with the severity of immunodeficiency as judged by the CD4+ cell count is presented here.

Materials and methods

Three hundred successive cases of ART-naive HIV-positive patients presenting with neurologic manifestations were enrolled in this study over a 3-year period. A written informed consent, specifically detailing the study, was taken from all of the patients along with prior approval from the Institutional Ethics Review Committee. The presence of the HIV infection was confirmed as per the National AIDS Control Organization guidelines. All of the cases underwent detailed clinical evaluation, followed by relevant laboratory investigations and appropriate neuroimaging, including computed tomography (CT) and magnetic resonance imaging (MRI) scans. On the basis of these results, the cases with OIs were then excluded from further study. Those cases in which the neurologic manifestations were due to concomitant systemic illness or medications were also excluded. The cases with no apparent evidence of OIs were considered to be due to the direct effects of the HIV infection and formed the study group.

Because HIV infection is known to affect all levels of the neuroaxis, these patients were divided into specific subcategories. These included: (1) CNS meninges, brain, and spinal cord; and (2) PNS anterior horn cells, radicles, peripheral nerves, neuromuscular junction, and the muscles. For each specific subcategory, multiple tests including relevant neuroimaging, serology, and electrophysiology were carried out to exclude the role of opportunistic/systemic diseases in their pathogenesis. The immune status was assessed on the basis of the CD4+ cell counts using a fluorescent-activated cell sorter count. HIV viral load could not be determined due to resource limitations.

Results

A total of 300 successive cases of patients with HIV/AIDS with neurologic manifestations were studied. These patients were selected from internal medicine, neurology, and retroviral clinics/wards, over a period of 3 years. Out of these, 233 cases revealed an evidence of an opportunistic infection involving the neuroaxis, while 67 cases (22.3%) were due to the direct effects of HIV infection per se. The cases, which were due to OIs, were then excluded from further study. Table 1 shows the distribution of cases, which were due to OIs or opportunistic cancers.

In the study group of patients with neurologic manifestations not due to opportunistic or concomitant diseases other than HIV, 74% of cases were males (n = 50) and 26% were females (n = 17). This gender distribution matches the demography of HIV-1 infection in India (M:F ratio = 3:1). As the epidemic continues to grow, we are seeing more and more females being infected through the heterosexual mode of transmission. Table 2 depicts the distribution of cases by age. Seventy-six percent of the cases were in the 1545 years age group. The prevalence rates shown in Table 2 are in concordance with the general age-specific prevalence rates for HIV-1 infection in India. The risk behavior for acquisition of HIV infection was analyzed; 92.5% of the cases were due to multipartner unprotected heterosexual exposure; 2 cases were attributed to intravenous drug use (IVDU), and there was a single case of documented vertical transmission.

Table 3 shows the distribution of patients into different categories depending on their clinical evaluation and CD4+ cell counts. This categorization format is the 1993 revised classification for HIV infection and expanded case definition for AIDS in adolescents and adults. The majority of our patients fell into category C (60%), and 65% of these cases were within the subcategory C3 as they had CD4+ cell counts < 200 cells/microliter (mcL). The addition of pulmonary tuberculosis as an AIDS-defining condition by the US Centers for Disease Control and Prevention (CDC) in 1993 has resulted in a larger-than-

Table 1: Distribution of Cases, Attributed to Opportunistic Diseases (n = 233)

Infection/Cancer	Number of Cases	Mean CD4+ Cell Count (cells/mcL)
Neurologic toxoplasmosis	61	150
Neurologic tuberculoma	48	212
Cryptococcal meningitis	51	114
TB meningitis	24	160
Progressivemultifocal leukoencephalopathy	20	108
Primary CNS lymphoma	8	54
TB arachnoiditis radiculopathy	3	140
TB osteomyelitis myelopathy	4	234
Neurologic cysticercosis	4	350
Cryptococcoma	3	110
CMV radiculopathy	3	94
Varicella-zoster radiculopathy	2	100
CMV encephalitis	1	32
Varicella-zoster leptomeningitis	1	212
TOTAL	233	

mcL = microliter; TB = tuberculosis; CNS = central nervous system; CMV = cytomegalovirus

expected number of cases being classified in India into subcategory C3 due to the already high prevalence of tuberculosis in the community/general population.

Stroke Syndromes

Strokes and transient neurologic deficits are commonly seen with HIV/AIDS. There were 20 cases of stroke that were apparently due to HIV infection per se. Ten patients had a CD4+ cell count between 200 and 500 cells/mcL, whereas 8 cases (40%) had a CD4+ cell count between 100 and 200 cells/mcL. The mean CD4+ cell count in the study was found to be 212 cells/mcL.

The causes of strokes in this study were varied (Table 4). Nine of the 20 cases were due to thrombotic occlusion of large vessels. Four cases were due to probable vasculitis (20%), and the remaining cases were caused by lacunar infarcts, transient ischemic attacks (TIAs), and intracranial bleeds.

The mechanism of the thrombotic occlusion of large vessels was difficult to pinpoint. A large number of causes

have been proposed, making it essential to now consider HIV as a prothrombotic state giving rise to strokes in relatively young people. Of the 20 cases in our study with HIV-related strokes, 15 were in the 1545 years age group. Due to the enormous costs involved, it was not possible to investigate the prevalence of specific known thrombophilic factors in these patients.

Vasculitis probably due to the HIV virus contributed to 20% (n = 4) of the stroke syndromes. These patients presented with focal deficits and advanced HIV disease. MRI with angiograms revealed evidence of a focal segmental narrowing of vessel walls, a feature of vasculitis. The cerebrospinal fluid (CSF) was examined for antibodies to varicella-zoster virus and cytomegalovirus as well as venereal disease research laboratory slide test (VDRL) titers, as these infections are known to cause vasculitis in the absence of systemic manifestations of the primary disease. However, CSF examination in these cases did not reveal any of these antibodies, thereby indicating that the vasculitis was probably due to the direct effects of the retrovirus.

Table 2: Distribution of Non-OI (HIV-Related) Cases by Age (n = 67)

Neurologic Manifestation	< 15 yrs	1545 yrs	4660 yrs	> 60 yrs
Brain				
Stroke	0	15	5	0
Demyelination	1	2	1	0
AIDS dementia	0	4	0	0
Aseptic meningitis/encephalitis	0	3	0	0
Venous sinus thromboses	0	3	0	0
Cranial neuropathy	0	7	2	0
Spinal cord involvement	0	3	2	0
Radiculopathies	0	2	1	0
Peripheral neuropathies	0	12	2	1
Myopathies	0	0	1	0
TOTAL	1	51	14	1
Percentages	< 1%	76%	20.8%	< 1%

OI = opportunistic infection; yrs = years of age

Two young patients with hemiplegia without any identifiable risk factors had lacunar infarcts in the basal ganglia and the internal capsule.

Demyelination
Demyelination affecting the spinal cord in HIV disease is well established, but of late, immune-mediated demyelination involving the brain is being reported with increasing frequency. Four of our cases had clinical features suggestive of a demyelinating disorder. The neuroimaging features were very different from those of progressive multifocal leukoencephalopathy, a close differential diagnosis.

Table 5 shows the clinical description and course of the cases of HIV demyelination.

AIDS Dementia Complex
AIDS dementia complex was seen in 4 patients. This disorder manifested as a subacute, progressive, subcortical dementia. All of the patients had advanced immune deficiency. The average survival from the time of diagnosis was 5 months. Table 6 demonstrates the profile of cases with AIDS dementia complex.

Cortical Venous Sinus Thromboses
HIV infection gives rise to a prothrombotic state. The potential contributing factors that have been identified are: (1) anticardiolipin antibodies; (2) low levels of protein S; (3) deficiency of heparin cofactor 2; and (4) vasculopathy.[1-3] There were 3 cases of cortical venous sinus thrombosis. The patients had moderate-to-advanced immune deficiency. They had no family history or previous episode of thrombophilia. Two of the 3 patients had low levels of protein S and positive anticardiolipin antibodies.

All 3 patients received heparin therapy followed by warfarin for 3 months, and showed significant improvement. CSF examination ruled out infectious etiologies of venous sinus thrombosis. The clinical profile of each of these cases is shown in Table 7.

HIV Neuropathy
There were 24 cases (38%) of neuropathy, 15 peripheral neuropathies and 7 cranial neuropathies (Table 8). Cranial neuropathies were identified in 9 patients. The most common cranial neuropathy was a self-limiting Bell's palsy, which was seen in 7 of the 9 cases, the remaining 2 being cases of polyneuritis cranialis.

Table 3: Classification of HIV Neurologic Manifestation Cases by US Centers for Disease Control and Prevention Categories (n = 67)

Manifestation	B1	B2	B3	C1	C2	C3
Brain						
Stroke	0	4	5	1	4	6
Demyelination	0	1	1	0	0	2
Aseptic meningitis	0	0	2	0	0	1
Venous sinus thrombosis	0	0	1	0	2	0
AIDS dementia complex	0	0	0	0	0	4
Cranial neuropathy						
Bell's Palsy	4	3	0	0	0	0
Polyneuritis cranialis	0	1	0	0	1	0
Spinal cord						
Vacuolar myelopathy	0	0	0	0	0	2
ATM	0	0	0	0	0	1
Myeloradiculopathy	0	0	0	0	0	2
Peripheral neuropathy						
Guillain-Barré syndrome						
AIDP	1	3	0	0	0	0
AMAN	0	1	0	0	1	0
AMSAN	0	0	0	0	1	1
Mononeuritis multiplex	0	0	1	0	1	0
DPSN	0	1	0	0	1	3
Radiculopathy	0	0	0	0	2	1
Myopathy	0	1	0	0	0	0
TOTAL	5	14	10	1	13	24

ATM = acute transverse myelitis; AIDP = acute inflammatory demyelinating polyradiculoneuropathy; AMAN = acute motor axonal neuropathy; AMSAN = acute motor and sensory axonal neuropathy; DPSN = distal predominantly sensory neuropathy (also known as distal symmetrical polyneuropathy and distal symmetrical peripheral neuropathy)

Table 4: Cases of HIV Stroke Syndromes (n = 20)

Type of stroke	CD4+ Cell Count (cells/mcL)			
	< 100	100200	200500	> 500
TIA	0	0	1	0
RIND	0	0	3	0
Large vessel thromboses	0	4	4	1
Vasculitis	1	2	1	0
IC bleeds	0	1	0	0
Lacunar strokes	0	1	1	0
TOTAL	1	8	10	1
% of total stroke syndromes	5%	40%	50%	5%

mcL = microliter; TIA = transient ischemic attack; RIND = reversible ischemic neurologic deficit; IC = intracranial

The most common cranial neuropathy seen was the benign seventh cranial nerve palsy (Bell's palsy). The cases of Bell's palsy were found to occur early in the HIV disease and often during initial seroconversion. Clinically they were indistinguishable from the classic Bell's palsy. The CD4+ cell count of affected patients ranged from 356 to 511 cells/mcL, with a mean of 457 cells/mcL. CSF examinations as well as neuroimaging in all of these cases were normal. The disease was self-limited, with most of the patients (85%) showing complete recovery within 2 weeks without any therapy. Only 1 patient who had presented with a low CD4+ cell count had partial recovery of his facial weakness.

There were 2 cases of mononeuritis multiplex (Table 8) thought to be secondary to vasculitis, of which only 1 could be confirmed by nerve biopsy. There were 5 cases of distal predominantly sensory neuropathy (Table 8). There were no cases of chronic inflammatory demyelinating polyradiculoneuropathy or diffuse infiltrative lymphocytosis syndrome identified.

There were 5 patients with distal symmetric predominantly painful sensory neuropathy, also known as distal symmetrical polyneuropathy and distal symmetrical peripheral neuropathy (Table 8). All of these cases were seen in advanced states of HIV/AIDS. The predominant manifestations in most (85%) were a painful burning sensation in the feet with late and mild involvement of the hands. The main abnormality found on clinical examination was loss of superficial sensations such as pain, tem-

Table 5: Cases of HIV Demyelination (n = 4)

Clinical presentation	Age	Sex	CD4+ Cell Count	Treatment	Status
Hemiplegia, neuroregression and visual loss	10 yrs	F	371	Nil	Relapsing remitting
Cerebellar syndrome	40 yrs	M	336	Antiretroviral therapy	Improved
Hemiplegia with visual loss	54 yrs	M	188	Steroids	Died due to aspiration pneumonia
Hemiplegia with facial palsy	34 yrs	M	320	Steroids	Improved

perature, and touch. In 1 case was the joint position and vibration sense lost. Sixty percent of cases had an absent ankle jerk. The neuropathy was bilaterally symmetrical in all cases. The mean CD4+ cell count in this study was 141 cells/mcL, while the range extended from 98 to 212 cells/mcL.

After HIV seroconversion, the polyclonal stimulation resulting in hypergammaglobulinemia has been reported to be associated with many immune-mediated conditions, such as Guillain-Barré syndrome and immune-mediated thrombocytic purpura. There were a total of 8 cases of the Guillain-Barré syndrome in this study (Table 8), of which 4 were identified on electrophysiology to be demyelinating and the remaining 4 were axonal variants: acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN). The clinical course was found to be no different from that of non-HIV cases (Table 9). Three patients could afford intravenous immunoglobulin (IVIG) and showed an excellent response to treatment. The remaining patients were managed conservatively, with only 1 requiring prolonged ventilator support. Two patients with the axonal form of the disease showed little improvement, while 1 patient was lost to follow-up. The CSF analysis in these patients did not show the classic albuminocytologic dissociation as expected at the end of the first week. Seven out of 8 patients had a mild mononuclear pleocytosis along with the raised protein levels.

HIV/AIDS Myelopathies

The spinal cord in HIV disease is frequently involved in advanced stages of immunodeficiency. We had 2 cases of vacuolar myelopathy, 2 cases of myeloradiculopathy, and a single case of acute transverse myelitis. In Western literature it has been found that there is a significant overlap between vacuolar myelopathy and the AIDS dementia complex. This has been explained by the cytokine mechanisms behind the origin of both entities, especially mediated by tumor necrosis factor (TNF)-alpha. However, in our study we did not find any overlap between the 2 conditions. Table 10 shows the spectrum of myelopathies seen in this study.

The single case that presented with acute transverse myelitis had a low CD4+ cell count: 56 cells/mcL. On MRI of the spine, he was found to have a large segment of cord inflammation of the spine and was subsequently treated with steroids. However, there has been no improvement at all. There were 2 cases of classic vacuolar myelopathy. They presented with a spastic ataxic syndrome not having a sensory level (ie, the neurologic lesions could not be localized to a particular segment of the central nervous system). There was a marked impairment of the joint position and vibration sense. The vitamin B_{12} levels in both of these patients were normal and the spinal MRI revealed subtle signal changes in the posterior columns of the spinal cord. None of these patients had any clinical evidence of the AIDS dementia complex.

Table 6: Cases of AIDS Dementia Complex (n = 4)

Stage of ADC	Age	Sex	Route of Transmission	CD4+ Cell Count(cells/mcL)	Duration of Survival
Stage 2	38	M	H	106	6 months
Stage 3	35	M	H	115	2 months
Stage 4	35	M	H	56	7 months
Stage 2	42	M	H	120	5 months

mcL = microliter; ADC = AIDS dementia complex; M = male; H = heterosexual

Table 7: Cases of HIV Cortical Venous Sinus Thrombosis (n = 3)

Sinus involved	Age	Sex	Mode of Transmission	CD4+ Cell Count(cells/mcL)	Treatment
Superior sagittal with transverse sinus	35 yrs	M	H	148	Heparin then warfarin
Superior sagittal with transverse and sigmoid sinuses	26 yrs	M	H	212	Heparin then warfarin
Superior sagittal and straight sinus	30 yrs	M	H	256	Heparin then warfarin

mcL = microliter; M = male; H = heterosexual

Radiculopathies
There were 3 cases of HIV radiculopathy. The cases were associated with moderate-to-advanced immunodeficiency. The CD4+ cell counts ranged from 186 to 265 cells/mcL. The mean CD4+ cell count was 217 cells/mcL. We were able to analyze the CSF of all 3 patients for cytomegalovirus by the polymerase chain reaction (PCR) technique. CSF in all 3 patients was negative for cytomegalovirus by PCR. The disease progression and course was slow, and hence it was concluded that in these patients the HIV infection probably caused the radiculopathy.

HIV Myopathies
There was a single case of proximal myopathy that was probably linked to the HIV infection. The patient was a 44-year-old man who presented with proximal muscle weakness. His CD4+ cell count was 465 cells/mcL and his creatine phosphokinase (CPK) enzyme levels were highly elevated. The patient had no OI and had never received antiretroviral therapy. He was given a short course of steroids and is showing good response. A muscle biopsy could not be done on the patient due to lack of consent.

Discussion
This study has shown that HIV-1 is indeed a neurotropic virus, which can produce a large variety of neurologic manifestations affecting all levels of the neuroaxis. Although OIs of the nervous system are still by far the most commonly seen manifestations,[1] the availability of good prophylactic and therapeutic medications for these OIs has meant that more features of direct HIV neuroinvolvement are being seen.

The HIV viral RNA and other component proteins have been demonstrated in neural tissues by processes such as in situ hybridization and immunocytochemistry.[1,2]

Table 8: Cases of HIV Neuropathy (n = 24)

Type of neuropathy	Males	Females	Total
Cranial neuropathy			
Bell's palsy	5	2	7
Polyneuritis cranialis	2	0	2
Peripheral neuropathy			
Guillain-Barré syndrome			
AIDP	4	0	4
AMAN	1	1	2
AMSAN	2	0	2
Mononeuritis multiplex	2	0	2
Distal predominantly sensory neuropathy	4	1	5
TOTAL	20	4	24

Table 9: Cases of Guillain-Barré Syndrome (n = 8)

Clinical features	Age/Sex	CD4+ Cell Count(cells/mcL)	Type of GBS	Therapy	Status
Ascending paraparesis	23 y/M	335	AIDP	IVIG	Improved
Quadriplegia requiring ventilator	30 y/M	420	AIDP	IVIG	Improved
Ascending weakness with neck muscle involvement	45 y/M	450	AMAN	Steroids	Improved
Quadriplegia	35 y/M	204	AMSAN	Nil	Mild improvement
Descending weakness with lower cranial nerve palsies	34 y/M	195	AMSAN	Nil	Mild improvement
Quadriparesis	33 y/M	456	AIDP	Steroids	Improved
Ascending muscle weakness	35 y/F	400	AMAN	IVIG	Mild improvement
Paraparesis	42 y/M	450	AIDP	Nil	Not available

GBS = Guillain-Barré syndrome; IVIG = intravenous immunoglobulin; AIDP = acute inflammatory demyelinating polyradiculoneuropathy; AMAN = acute motor axonal neuropathy; AMSAN = acute motor and sensory axonal neuropathy

They have predominantly been isolated from the microglial cells, giant cells, and capillary endothelial cells.[3] The virus appears to enter the brain via the infected macrophages, a pathogenic mechanism described by the "Trojan horse hypothesis."[4] The total number of infected cells is low, but the virus appears to induce widespread neuronal dysfunction predominantly through cytokine release.

Strokes and TIAs are commonly seen in patients with HIV disease. Although a large number of them are due to OIs, in approximately half there is no cause discernable apart from the HIV disease itself. Clinical evidence of strokes and TIAs has been found in approximately 1.5% of patients with advanced HIV disease.[5,6] Brew and colleagues[5] found the mean CD4+ cell count to be 130 ± 80 cells/mcL, with most having CD4+ cell counts < 50 cells/mcL. These figures were derived from studies carried out in ART-naive patients, very similar to the population base in our country. In our study, 29.8% of non-OI manifestations were stroke syndromes. Ten patients (50%) had a CD4+ cell count between 200 and 500 cells/mcL, whereas 8 cases had a CD4+ cell count between 100 and 200 cells/mcL. The mean CD4+ cell count in the study was found to be 212 cells/mcL. Seventy-five percent of the patients had a young stroke, aptly proving the fact that HIV disease results in a prothrombotic state. This prothrombotic state is due to a complex mix of effects of anticardiolipin antibodies, low protein S levels, and altered heparin cofactor II levels.[5-9] In addition to this, vasculitis produced by the virus itself tends to be prothrombotic due to the endothelial dysfunction, resulting in a significant overlap between the two. In advanced HIV infection,

Table 10: Cases of HIV Myelopathy (n = 5)

Age(yrs)	Sex	Route of Transmission	CD4+ Cell Count	Diagnosis	Status
24	M	H	56	ATM	Stable
40	M	IVDU	229	Vacuolar myelopathy	Progressing
34	M	H	120	Vacuolarmyelopathy	Expired due to PCP
29	M	H	98	Myeloradiculopathy	Expired
29	M	H	178	Myeloradiculopathy	Stable

M = male; H = heterosexual; ATM = acute transverse myelitis; PCP = Pneumocystis carinii pneumonia

excessive inappropriate elaboration of TNF alpha and interleukin-1 add to the thrombophilia.[10]

In HIV disease most cases of demyelination involve the spinal cord. In this study we found 4 cases (5%) that presented with CNS demyelination. Berger and coworkers[11] reported 7 cases of multiple sclerosis-like illness in HIV-positive patients. It is found to occur in the early phases of the retroviral infection, where there is a polyclonal hypergammaglobulinemia. The antibodies cross-react with myelin in the CNS, resulting in the demyelination. As the HIV disease progresses, with advancing immune deficiency, it is observed that there is an improvement in the clinical status of these patients.[12] This probably arises from the fact that, with advancing immune deficiency, the ability of the body to mount an immune-mediated response progressively gets disabled. In this study, 2 out of 4 patients had marked improvement. One of them had a relapsing-remitting form of disease, and 1 died due to *Pneumocystis carinii* pneumonia.

In this study we found that 5% of the non-OI cases were due to the AIDS dementia complex (ADC). Increasingly more number of cases of ADC are going to be seen, due to the availability of good prophylaxis and therapy for OIs. Studies from western countries have shown that 20% to 30% of patients with advanced HIV infection go on to develop ADC.[13]

Wadia and associates[14] reported 21 cases of ADC of a total of 481 cases (4.3%) of HIV patients with neurologic manifestations. The advent of antiretroviral therapy (HAART) in western countries has led to significant reduction in the incidence of ADC.[15]

The bulk of the cases in this study, 38%, were constituted by HIV neuropathy. It has been shown in different studies that between 10% and 35% of HIV-infected individuals develop a neuropathy that can be ascribed to the HIV infection itself.[16,17] Histopathologic abnormalities in peripheral nerves have been found in over 95% of patients dying with AIDS.[18] Neuropathy is found to occur at all stages of HIV infection. During seroconversion we saw cases of facial neuropathy and acute inflammatory demyelinating neuropathies. As the disease advanced, mononeuritis multiplex, secondary to vasculitis and polyneuritis cranialis, were evident. Finally, with advanced HIV disease, there were cases of distal painful predominantly sensory neuropathy. There were 8 cases of the Guillain-Barré syndrome. One important feature seen in all of these patients with Guillain-Barré syndrome was that their CSF analysis at the end of the first week did not show the classic albuminocytologic dissociation. All studies have shown either a raised protein level and or a mononuclear pleocytosis.[19,20] Cornblath and colleagues[19] found

the mean CSF cell count to be 23 cells/mcL, with a maximum of 43 cells/mcL. In our study, all of the patients had a slightly elevated CSF protein content, and the CD4+ cell count ranged from 0 to 30 cells/mcL, with a mean of 15 cells/mcL.

By performing this study, we have realized that this disease is constantly evolving and placing new challenges in front of the physician and the society. Right from its detection in 1981 up to the new millennium, every single year that has passed by has seen this virus evolve and remain elusive to medical therapy. Billions of dollars have been spent in both prevention and cure, but still the epidemic continues to grow, especially in third-world countries. In the year 2000, the United Nations Security Council discussed this disease as an issue of global security in their annual meeting. The youth of countries across the globe were succumbing to the effects of the HIV infection destroying the economic and social fabric of these countries.

In the current world scenario, with the advent of HAART and effective chemoprophylaxis for OIs, there has been a significant impact on the disease. However, as the incidence of the opportunistic manifestations was reduced by chemoprophylaxis, an entire spectrum of non-OI manifestations and drug related toxicities evolved.

From a physician's perspective, these non-OI manifestations are difficult to diagnose because of the lack of specific tests and limited knowledge that is available. Most of these non-OI neurologic manifestations are crippling, imposing huge burdens on the patient's family and the healthcare system.

The treatments of most of these manifestations are limited. The initial immune-related phenomenon, such as the Guillain-Barré syndrome, could be dealt with by using immune globulins, plasmapheresis, and steroids. The costs of immune globulins are exorbitant, and most institutions do not offer plasmapheresis facilities to HIV-positive patients. Use of corticosteroids in HIV patients for both Guillain-Barré syndrome and demyelinating illnesses always has to be done with apprehension, as these patients are already immune-compromised and prone to infection.

The ideal way to assess the relationship between the non-OI neurologic manifestations and HIV disease progression is by estimating the plasma and CSF viral loads. In India today the only affordable methodology is the estimation of the CD4+ cell counts. There are laboratories that estimate the plasma viral load, but the costs have proven to be prohibitive. As far as the CSF viral load is

concerned, this technology remains to be introduced in the country.

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Authors and Disclosures

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