

A Study on Pattern of Neurological Complications in Human Immunodeficiency Virus Infected Patients Attending a Tertiary Care Center in South Tamil Nadu, India

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Abstract

background: Highly active antiretroviral therapy and adequate chemoprophylaxis for opportunistic infections for human immunodeficiency virus (HIV) infected patients have led to increasing survival in people living with HIV/AIDS. The nervous system is among the most frequent and serious targets of HIV infection. 40–70% of all persons infected with HIV develop symptomatic neurological disorders. This study was undertaken to study the diverse clinical presentations of neurologic abnormalities in HIV patients admitted in a tertiary care center in South Tamil Nadu.

Materials and Methods: A prospective study was conducted for 2 years in HIV-infected patients who were admitted at a tertiary care hospital were subjected to thorough neurological evaluation and those with symptoms referring to neurological illness were enrolled, and clinical signs and symptoms were noted. CD4 counts of all the cases were performed by FACS counter, and neuroimaging study was performed on necessary cases.

Results: A total of 71 cases with 74.6% males and 25.4% females were enrolled. Mean age for males 34.6 years; for females 31.1 years. Headache was the most common symptom (67.3%) followed by altered sensorium (40.8%). Central nervous system (CNS) tuberculosis (TB) is the most common disease in patients presenting with neurological abnormalities (42.25%). There is a significant correlation between the levels of CD4 counts and the type of neurological manifestations.

Conclusions: Incidence of neurological illness in HIV infection was 41.7%. Opportunistic infections are the leading cause of neurological disorders in our population. Meningitis was the most common neurological presentation (57.7%). TB is the single most common organism affecting CNS (42.2%).

Key words: CD4 count, Cryptococcal meningitis, Human immunodeficiency virus, Tubercular meningitis

INTRODUCTION

On the cusp of the fifth decade of the AIDS epidemic, human immunodeficiency virus (HIV) is still one of the leading infectious killer claiming >25 million lives over the past 30 years. In 2017, there were approximately 36.9

million people living with HIV, >2/3rd living in sub-Saharan Africa and Southeast Asia.^[1]

HIV/AIDS causes a wide spectrum of disease manifestations. The nervous system is among the most frequent and serious targets of HIV infection. 40–70% of all persons infected with HIV develop symptomatic neurological disorders. Although nervous system involvement typically occurs with profound immunosuppression and in the presence of other AIDS defining illnesses, in 10–20% of HIV seropositive persons it heralds AIDS. All levels of neuraxis can be involve including the brain, meninges, spinal cord, peripheral nerve, and muscle. Central nervous system (CNS) infections

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are the third most common cause of morbidity and the second most common cause of mortality in HIV patients. Neurological illness may occur throughout the course of infection from seroconversion to full blown AIDS.

The neurological problems fall into four major categories; (1) neurological disease caused by HIV itself, (2) HIV-related neoplasms, (3) opportunistic infection of the nervous system, and (4) adverse effects of medical therapy.

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.

The pattern in India appears to differ from the classical literature in that neurotuberculosis leads the list of opportunistic infections, and regional variability has been reported within India.^[2,3] A study of the various 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

All HIV-infected patients who were admitted in TVMC Hospital between October 2016 and September 2018 were subjected to thorough neurological evaluation, and those with symptoms referring to neurological illness were enrolled in this study after informed consent. Hospitalized patients with neurological signs and symptoms who were screened based on clinical clues and confirmed to have HIV-1 and/or HIV-2 infection (seropositive) by two HIV test systems (Rapid/ELISA/Western Blot) were also enrolled. Data were collected in a pre-tested pro forma by meeting the objective of the study. A detailed history, physical findings with thorough neurological examination and necessary investigations were recorded. Treatment and outcome were not included in this study.

All patients with neurological symptoms were individualized and were subjected to the investigations listed based on clinical findings. Routine hematological, biochemical investigations, and CD4 counts were done in all the cases enrolled in the study. CD4 count was done to all patients. Cerebrospinal fluid (CSF) analysis including protein, glucose, cell count and type, AFB, Gram stain, and India Ink preparation, was performed in all the cases of meningitis. Neuroimaging (computed-tomography/magnetic resonance

imaging) was performed whenever required as per study protocol. Serology to detect antibody to Toxoplasma, cytomegalovirus was done in suspected cases.

Inclusion Criteria

Adults presenting with neurological manifestations and diagnosed to be HIV seropositive.

Exclusion Criteria

Patients with pre-existing neurological disease immunocompromised state due to any other cause and children <14 years of age.

Statistical Analysis

Following statistical methods were employed in the present study.

1. Contingency coefficient analysis
2. Chi-square test
3. Independent samples *t*-test
4. One-way ANOVA
5. All the statistical operations were done through SPSS for Windows, Version 10.0 (SPSS Inc., 1999, New York) (Statistical Presentation System Software).

RESULTS

A total of 170 seropositive HIV patients were hospitalized in TVMCH between October 2010 and September 2011. 71 patients had neurological manifestations among the 170 patients were enrolled in this study. The prevalence of neurological manifestations among hospitalized HIV patients is 41.7%.

Age and Sex Distribution

- 53 males (74.6%) and 18 females (25.4%).
- Male: female ratio is 2.94:1
- Mean age for males 34.6 years; for females 31.1 years.
- 92.95% between 15 and 45 years of age.
- Majority of the patients with neurological manifestations in our study were between 31 and 40 years of age (53.5%).
- Only six patients were unmarried (8.5%).
- Married 91.5%; male 49: female 16
- In our study, most of the patients were daily laborers (26.7%) and drivers (25.3%).
- Majority of the patients were from lower socioeconomic class [Table 1 and Figure 1].

Mode of Transmission

- Heterosexual transmission was predominant in most patients.
- The various routes of transmission in multiple transmission group were blood transfusion, surgery, and contact with CSW in various combinations.

- 39.4% of the cases were diagnosed to have HIV before admission.
- Neurological manifestations heralded the onset of HIV in 60.6% of the cases [Table 2 and Figure 2].

Neurological Symptoms

Table 3 shows the various clinical presentations and their frequency in the patients having neurological manifestations.

- Headache was the most common symptom (67.3%) followed by altered sensorium (40.8%).
- Headache, as observed in this study, was primarily due to a meningeal infection, tuberculosis (TB), and cryptococcal meningitis being the most frequent [Figure 3].

Neurological Signs

- Signs of meningeal irritation were present in 57.7% of the cases. This includes 15 cases of cryptococcal meningitis and 22 cases of CNS TB.
- Nearly 40.8% had altered mentation that included 4 patients with cognitive dysfunction.

Table 1: Age*sex cross-tabulation

Age	Sex		Total
	Male	Female	
<20			
Count	1	0	1
% Within sex	1.9	0	
21–30			
Count	17	4	21
% Within sex	32.1	22	
31–40			
Count	26	12	38
% Within sex	49	66.6	
41–50			
Count	9	2	11
% Within sex	16.9	11.1	
Total	53	18	71

Table 2: Presentation old/new cases

HIV serology positive	Frequency (%)
Old	28 (39.43)
New	43 (60.56)
Total	71 (100)

Table 3: Neurological symptoms

Symptoms	Frequency (%)
Headache	48 (67.36)
Altered sensorium	29 (40.8)
FND	17 (23.9)
Seizures	14 (19.7)
Sensory	7 (9.8)
Behavioral	5 (7.0)

- Cranial nerve involvement was seen in 15 patients [Table 4 and Figure 4].

Disease Pattern

- CNS TB is the most common disease in patients presenting with neurological abnormalities (42.25%). 11 of these patients had tuberculoma.
- 41 patients presented with meningeal signs. 89.5% of TB meningitis and 93.75% of cryptococcal meningitis had features of meningeal irritation [Table 5, Figure 5 and 6].

CD4 Count Correlation

- CD4 count levels in patients with neurological symptoms ranged from 12 to 482 with an average of 115.1. The average CD4 levels in a patient without neurological manifestations are 217.7. There is a statistically significant difference between the group (independent group *t*-test $P = 0.003$).

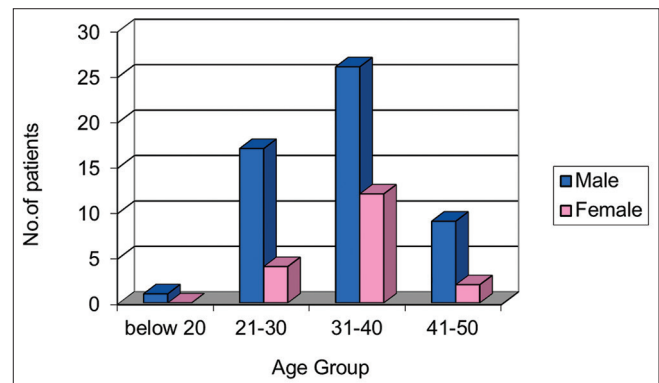


Figure 1: Age-sex distribution

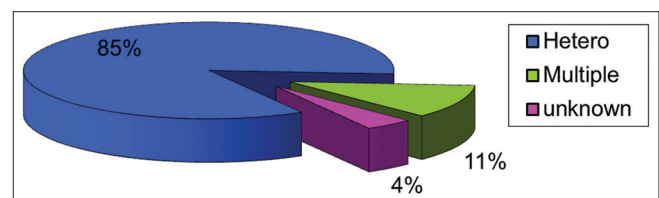


Figure 2: Mode of transmission

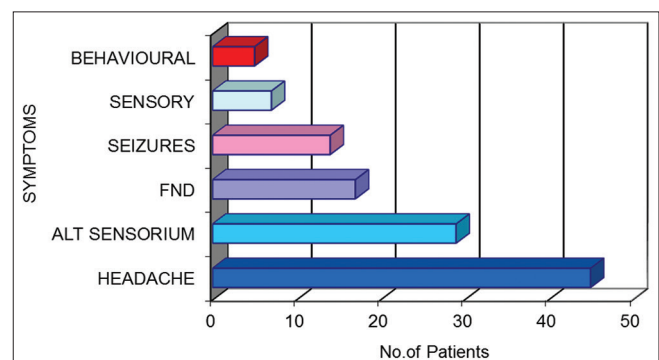


Figure 3: Neurological symptoms

Table 4: Neurological signs

CNS signs	Frequency (%)
HMF	34 (47.8)
Cranial nerve	15 (21.1)
Abnormal fundus	11 (15.5)
Motor	17 (23.9)
Sensory	7 (9.8)
Cerebellar	1 (1.4)
Meningism	41 (57.7)

CNS: Central nervous system

Table 5: Disease pattern

Diagnosis	Frequency (%)
Cryptococcosis	16 (22.53)
TBM	19 (26.76)
Tuberculoma	11 (15.49)
HIV Encephalopathy	2 (2.81)
Herpes zoster	2 (2.81)
Transverse myelitis	1 (1.4)
CVA	7 (9.86)
Bell's palsy	2 (2.81)
Meningoencephalitis	2 (2.81)
PML	1 (1.4)
Peripheral neuropathy	4 (5.63)
ADC	2 (2.81)
Toxoplasmosis	2 (2.81)
Total	71 (100)

Table 6: CD4 count

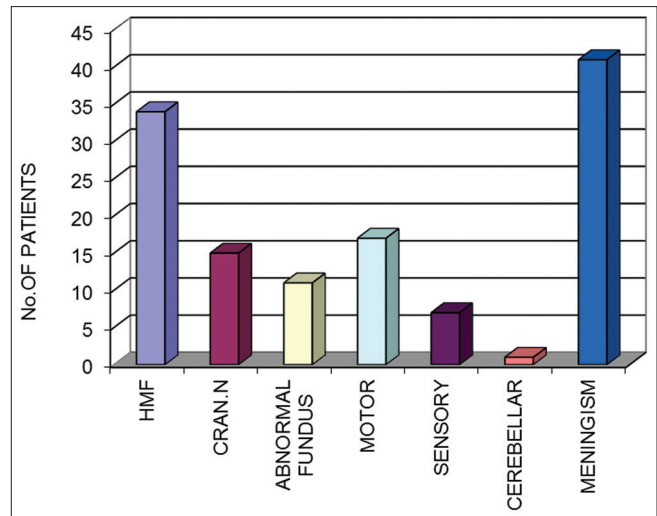
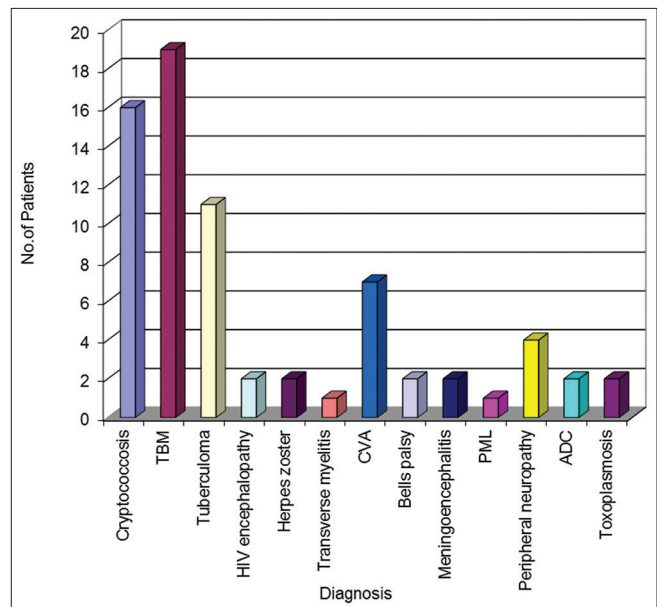
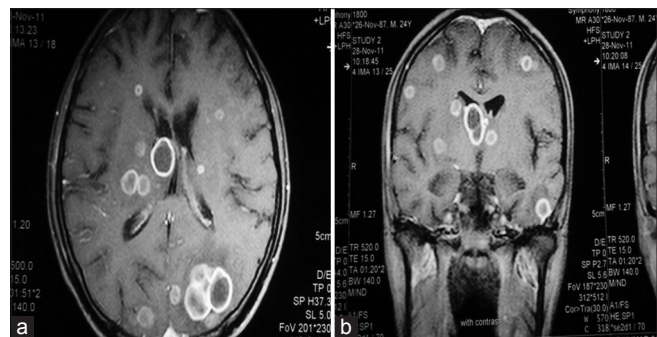
Study population	CD4 Count
	Mean±SD
Patients with neurological manifestation	115.1±86.9
Patients without neurological manifestation	217.7±08.1

- In this study, 16 patients were diagnosed to have cryptococcal meningitis based on CSF India ink preparation. Mean age 30.8 years, male: female ratio 2.2:1.
- The mean CD4 count of patients with cryptococcal meningitis was 51.6 ± 22.9 [Tables 6-8].

DISCUSSION

Neurological complications were seen in 20% of patients with HIV attending the outpatient clinic and in 44.5% of in-patients in a study by Wadia *et al.*^[4] in Pune. In a study by Millogo *et al.*,^[5] of the 686 patients admitted 101 (14%) had neurological manifestation.

The age ranged from 18 to 48 years. Mean age was 32 years (Male 34.6; Female 31.1), the majority of the patients (92.95%) falling in the economically productive age group of 20–45 years. Out of 71 patients 53 were male (74.6%) 18 were female (25.4%). Male: female ratio is 2.94:1. This

**Figure 4: Central nervous system signs****Figure 5: Disease pattern****Figure 6: (a and b) Magnetic resonance imaging showing multiple enhancing lesions in toxoplasmosis**

gender distribution matches the demography of HIV-1 infection in India (Male: female ratio = 3:1).^[6]

Table 7: Mean CD4 count levels

Neuro diagnosis	CD4 (mean±SD)/μL
CNS tuberculosis	97.3±24.3*
Cryptococcosis	51.6±22.9*
CVA	116.4±41.3
Toxoplasmosis	21±2.8
Peripheral neuropathy	155.5±26.6*

*P value significant. CNS: Central nervous system

Table 8: CD4 counts in various diseases

Diagnosis	CD4 Count/μL		
	<100	100–200	200–500
CCM	16	0	0
TBM	7	12	0
Tuberculoma	6	5	0
CVA	2	4	1
Peripheral neuropathy	0	3	1
Herpes zoster	0	1	1
Toxoplasmosis	2	0	0
Bell's palsy	0	2	0
ADC	0	1	1
HIV encephalopathy	0	1	1
Meningoencephalitis	0	1	1

John *et al.*^[7] in his Vellore based study observed male to female ratio of 4.26:1. Low figure of female infection rate is due to the admission pattern in most hospitals and social pattern (lifestyle) in our society where females are decreased to household activities and socialize less compared to males.

Predominantly heterosexual transmission was observed (84.5%). Multiple modes of transmission were thought of in 4 patients (11.3%), whereas in 3 patients the exact mode of transmission could not be ascertained. The various routes of transmission in the multiple routes transmission group of patients were blood transmission, surgery, and contact with commercial sex workers in various combinations. Multiple partners and contact with CSW were the cause of heterosexual transmission; this is in contrast to the western studies where homosexual transmission is more common.^[8,9] The disparity between the studies reported in the western literature and Indian studies can be explained by the different cultures and pattern of sexual activity in the respective society.

43 patients (60.56%) who presented to us with various neurological disorders were tested to be HIV positive after admission to the ward. The rest (28) were already diagnosed at the time of admission. McArthur *et al.*^[9] reported that 10% of all AIDS patients in their study presented with complaints referable to the nervous system. Levy *et al.*^[8] in their study in San Francisco reported that 1/3rd of their patients had neurological disorders as their presenting symptoms. Neurological disease is the 1st manifestation of AIDS in 10–20% symptomatic HIV infection.^[10]

Headache was the most common symptom seen in 48 patients (63.3%) that included 22 cases of CNS TB and 15 cases of cryptococcal meningitis, followed by altered sensorium in 40.8%, FND in 23.9%, and convulsion in 19.7% of the patients.

Among other symptoms, fever was present in 59% (42) patients that included 13 cases of cryptococcal meningitis and 24 cases of CNS TB, and significant weight loss in approximately 53.5% (38) patients. Signs of meningeal irritation were present in 57.7% of patients (41). Out of these 15 had *cryptococcal* meningitis, 17 had TBM, 5 had tuberculoma (not confirmed by biopsy), and remaining were diagnosed as Meningoencephalitis, CVA, encephalopathy. Cranial nerve involvement was seen in 15 patients. 7 were associated with CVA, two with Bell's palsy, four with TBM one each with cryptococcal meningitis and herpes zoster.

Focal neurological deficit was seen in 17 patients. Of which 12 had hemiparesis, 2 Bell's palsy and one each of paraparesis and monoparesis. In the 17 patients with focal neurological deficits 7 were due to CVA, one paraparesis due to transverse myelitis and others due to TBM and space-occupying lesions.

Nearly 87.3% of the patients with neurological symptoms had CD4 count <200.

CD4 count ranged from 12 to 99 in cryptococcal meningitis and from 54 to 141 in CNS TB. The mean CD4 count of patients with cryptococcal meningitis was 51.6 ± 22.9.

Statistically significant ($P < 0.03$) difference of CD4 count was observed between the group of patients with cryptococcal meningitis and who did not have any neurological illness.

Mean CD4 in cryptococcal meningitis was less than TB meningitis indicating the occurrence of cryptococcal meningitis in patients with advance immunosuppression.

With the advent of HAART, the incidence of opportunistic infections decreased remarkably in the west with noninfectious etiologies leading the list of neurological manifestations. However, in countries like India where the prevalence of opportunistic infections is high, it is not surprising to see them leading the list of etiology of neurological conditions^[2,3,11] as observed in our study (51/71, i.e., 72%). Since TB is the most common opportunistic infection in HIV disease in India, it would be expected to involve the CNS frequently and was the most frequent cause of meningitis in our study. Most Indian studies document tubercular meningitis as being more common than cryptococcal meningitis.^[4,12]

The most common neurological complication of HIV infection in this study was due to tubercular involvement of the nervous system. It was seen in 30 patients (42.2%). Of them, 19 had tubercular meningitis and 11 had intracranial tuberculomas. The diagnosis was made based on clinical, imaging CSF analysis and response to treatment. The mean age at diagnosis was 34.68 years. TB was the presenting manifestation in 13 cases. 4 patients had focal deficits due to vasculitis/mass lesion.

The incidence of toxoplasmosis in different studies has been from 1.33% to 3.3%.^[2,3,11] The incidence in the present study was 2.81%, comparable to rest of Indian studies. Of the 2 patients, one presented with hemiparesis other with fever and headache. Both the patients had low CD4 count 19–23. Toxoplasmosis is diagnosed in these patients based on clinical, radiological grounds with elevated IGM antibodies. One of the interesting features is that CSF picture was normal in both of our patients.^[6,7]

Two patients in our study had herpes zoster. The diagnosis of herpes zoster was made clinically on the basis of the characteristic presentation of vesicles in the dermatomal or disseminated pattern. The first patient had thoracic dermatomal distribution and the second one presented with trigeminal distribution. Herpes zoster was presenting disease in the first patient HIV infection detected after hospitalization. The incidence of herpes zoster in HIV infection has been reported to be 11.8% by Das *et al.*^[13]

One patient in our study was diagnosed to have progressive multifocal leukoencephalopathy (1.4%). The patient had involuntary movements involving right upper and lower limbs with memory loss on presentation. Mini-mental score of the patient was 20. CSF analysis showed no abnormalities

Many of the patients in our study had impaired cognitive functions in ranging degrees as seen clinically as well as by psychological testing. However, the presence of opportunistic infection was on exclusion criteria for the diagnosis of HIV dementia. Hence, only 2 patients (2.81%) 1 males and 1 female were diagnosed to have AIDS dementia complex in this study by psychological analysis and Mini-mental scoring system. CSF analysis was normal, with CD4 counts 381–189. CT scan showed

cerebral atrophy in one patient and normal in other. McArthur *et al.*^[9] reported incidence of 7.3% in AIDS. They also reported increased incidence in homosexual man and increase with age.

Peripheral neuropathy was found in 4 patients. Of these 2 patients were on stavudine based ART and two patients were not on ART. Patients with peripheral neuropathy had a mean CD4+ level of $155.5 \pm 26.6/\mu\text{l}$. The predominant manifestations in most were a painful burning sensation in the feet with late and mild involvement of the hands. The patients with peripheral neuropathy had a relatively higher level of CD4+ counts compared with patients having other neurological diseases. Nerve conduction studies in these subjects showed distal sensory polyneuropathy.

Unilateral infranuclear facial palsy was observed in two young men with high-risk behavior. Both the patients were positive for antibodies to HIV. The CD4 count was 190–203/ μl seven patients in our study presented with cerebrovascular complications (9.86%). All seven patients presented with hemiparesis and their CT brain showed middle cerebral arterial territory infarct in 5 of the patients and two young patients with hemiplegia without any identifiable risk factors had lacunar infarcts in the basal ganglia and the internal capsule.

Deshpande and Patnaik^[14] have reported 7.67% incidence of CVA in his study with the majority of cases due to thrombotic occlusion of large vessels and vasculitis. Thorat *et al.*^[15] reported 16.6% of cerebrovascular events. Stroke mechanisms are variable in HIV-infected patients, with a relatively high incidence of vasculitis and hypercoagulability.^[16] Cerebral granulomatous angiitis due to HIV infection could result in vascular occlusive disease [Table 9 and 10].

The mean CD4 count of the cases in the study group was 115.1 ± 86.9 cells/mm³ which is found to be lower than most of the studies. The mean CD4 count of CNS TB is 97.3 ± 24.3 ; cryptococcosis is 51.6 ± 22.9 ; for cerebrovascular accidents is 116.4 ± 41.3 ; and for toxoplasmosis is 21 ± 2.8 . Studies have also reported the presence of neurological complication as well as other clinical manifestations associated with decreased CD4

Table 9: Neurological manifestation comparison

Symptoms/sign (number of patients)	CCM n=16 (%)	TBM n=19 (%)	Toxoplasma n=2 (%)	CVA n=7 (%)	Tuberculoma n=11 (%)
Fever (42)	13 (81)	18 (95)	1 (50)	1 (14)	6 (54)
Headache (45)	15 (94)	15 (79)	1 (50)	4 (57)	7 (64)
Focal neurological deficit (17)	1 (6.3)	3 (15.8)	0 (0)	7 (100)	6 (54)
Meningeal signs (41)	15 (93.5)	17 (89)	1 (50)	1 (14)	5 (45.5)
Seizure (14)	5 (31)	6 (32)	1 (50)	0 (0)	2 (18.2)
Altered sensorium (29)	13 (81)	11 (58)	0 (0)	1 (14)	0 (0)
Papilledema (11)	3 (18)	6 (32)	0 (0)	0 (0)	2 (18.2)

Table 10: Neurological diagnosis comparison of various studies in literature

Neurodiagnosis	Our study % n=71	Teja et al. ^[17] n=1606	Deshpande and Patnaik ^[14] n=300	Throat et al. ^[15] n=102	Levy et al. ^[8] n=318
CNS infections	72	39.4	47	39.22	32.39
Tuberculosis	42.25	25.06	8	5.04	<1
Cryptococcus	22.53	10.95	17	5.99	5.03
Toxoplasma	2.81	9.25	20.33	19.66	5.66
SOL	18.3	27.5	21	0.24	3.45
CMV	-	-	1.33	0.72	11.01
Peripheral neuropathy	5.63	-	8	4.9	7.86
Myopathy	-	-	0.33	-	0
Stroke	9.86	-	7.67	16.6	0.63
HAND	2.81	8.03	1.33	4.9	-
PML	1.4	1.7	6.67	3.9	0.63

count and increased viral load which is consistent with our study and secondary manifestations were more common in cases with CD4 counts <100 cells/mm³.

CONCLUSIONS

1. Incidence of neurological illness in HIV infection in our study was 41.7%.
2. Neurological manifestations heralded HIV in 62% of patients.
3. Heterosexual transmission is the major mode of transmission.
4. Opportunistic infections are still the leading cause of neurological disorders in our population.
5. Meningitis was the most common manifestation, (>57%) 41/71 patients comprising 15 cases of cryptococcal meningitis and 17 cases of tubercular meningitis.
6. Neuro TB is the most common disease affecting the nervous system followed by cryptococcal infection.
7. There is a significant correlation between the levels of CD4 counts and the type of neurological manifestations of HIV infection.
8. Neurological disorders with HIV infection might serve as an indicator for advanced HIV infection, immunosuppression, and decreased CD4 counts.
9. Neuropsychological assessment is mandatory for all HIV-positives patients.

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