ORIGINAL RESEARCH PAPER

General Medicine

CLINICAL PROFILE OF CENTRAL NERVOUS SYSTEM OPPORTUNISTIC INFECTIONS IN PEOPLE LIVING WITH HIV/AIDS

KEY WORDS: Opportunistic Infection, PLHA, HIV, Tubercular meningitis, Cryptococcal meningitis

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ABSTRACT

Background: Neurological involvement in HIV/AIDS accounts for significant degree of morbidity in a high percentage of people which as per some studies account for 5% to 15% of hospitalizations in PLWHA.[1] A clinical spectrum different from Western countries is expected in India, in view of different socioeconomic, cultural and demographic factors. **Aims and Objectives:** To study the clinical profile of central nervous system opportunistic infections in PLWHA. **Materials and Methods:** Study setting – Inpatient Department of Medicine of a tertiary care hospital in Jaipur, Rajasthan between July 2022 to February 2024; clinical profile of 64 patients admitted with neurological symptoms and/or signs associated with HIV/AIDS were studied. **Results:** Mean age 32.89 ± 9.21 years (range 18-61 years) and median age of our patients was 32.5 years. Subjects in our study were 42.18 % males and 57.81 % females. 34 patients in our study had CNS tuberculosis, 11 patients had CNS toxoplasmosis, 14 patients had Cryptococcal meningitis, and 5 patients had Progressive multifocal leukoencephalopathy. Headache was the most common presenting symptom. Four patients (three tuberculous meningitis and one cryptococcal meningitis) were lost to follow up after discharge. Total of 15 patients expired in our study. Mortality rate were as follows: CNS tuberculosis 19.3%, CNS toxoplasmosis 18.1%, Cryptococcal meningitis 38.4%, Progressive multifocal leukoencephalopathy 40%. Mean CD4 count of expired patients was 46.33 ± 30 cells per mm3 while mean CD4 count of all patients included in our study was 105.93 ± 77.17 cells per mm3. **Conclusions:** 1) Predominantly young adults between age group of 21 to 40 years are affected by central nervous system opportunistic infections in HIV patients. 2) Tuberculosis is the most common central nervous system opportunistic infection in our study. 3) Disseminated tuberculosis in people living with HIV/AIDS have poor mortality outcome when compared to patients with CNS tuberculosis. 4) CNS toxoplasma and cryptococcal meningitis have similar incidence in our study but prognosis differs. 5) Patients with progressive multifocal leukoencephalopathy had the worst mortality rate. 6) Low CD4 count (< 50 cells per mm3) in the presence of any central nervous system opportunistic infection in HIV patients is associated with high mortality rate. (p< .00001)

INTRODUCTION

The disease was first recognized in 1981 when Michael S. Gottlieb et al at the UCLA school of medicine reported unexplained occurrence of Pneumocystis carinii pneumonia in 5 previously healthy homosexual men in Los Angeles and Kaposi's sarcoma in 26 previously healthy homosexual men in New York and Los Angeles.[2] Neurological involvement was confirmed in 1985, when isolation of infectious human immunodeficiency virus type 1 (HIV-1) from brain tissues and cerebrospinal fluid (CSF) of patients with the disease and the detection of the HIV-1 genome in the brain strongly suggested that this virus is directly responsible for some of the neurological disorders found in patients with AIDS.[3] HIV-associated neurocognitive disorder (HAND), Vacuolar myelopathy, Cerebrovascular disease, Aseptic Meningitis are few central nervous system manifestations caused directly by the virus. Neurological complications in people living with HIV/AIDS may also be secondary to opportunistic infections such as tuberculous meningitis, toxoplasma meningoencephalitis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, Cytomegalovirus encephalitis, primary CNS lymphoma, etc. [4] Nearly 30 years after the advent of antiretroviral therapy (ART), CNS opportunistic infections remain a major cause of morbidity and mortality in HIV-positive individuals. [5]

Aims And Objectives

Aim: To study the clinical profile of various central nervous system opportunistic infections in people living with HIV/AIDS.

Objectives:

1. To study the epidemiological factors of various central nervous system opportunistic infections in people living with HIV/AIDS.
2. To study the clinical features and outcome of various central nervous system opportunistic infections in people living with HIV/AIDS.
3. To study the relationship between CD4 count and central nervous system opportunistic infections in people living with HIV/AIDS.

MATERIALS AND METHODS

Study Setting:

This study was conducted in the Department of General Medicine in a tertiary care hospital of Jaipur.

Patients admitted in medicine wards with neurological complications associated with HIV infection were studied prospectively between August 2022 to February 2024. Detailed clinical history and physical examination was done.

Inclusion Criteria:

Indoor patients in medicine wards with signs and symptoms

of central nervous system infections who-
1. Are known HIV positive
2. Are detected to be HIV positive after admission
3. Are above 18 years of age and give valid and written informed consent

Exclusion Criteria:
1. Seropositive patients with history of neurological diseases like cerebrovascular accidents due to other comorbidities such as diabetes mellitus and hypertension, and with history of epilepsy, parkinsonism.
2. Encephalopathy unrelated to HIV and opportunistic infections.
3. Patients who do not give their consent

Investigations:
Complete blood count, Liver function test, Renal function test, Serum electrolytes, Urine routine examination, Urine culture sensitivity, Blood culture sensitivity, CD4 count, HIV- I & II, HBsAg, HCV serology, was done for all patients. All patients underwent Computed Tomography scan of brain and CSF analysis. CSF analysis included CSF Protein, glucose, cell count, ADA and AFB smear for all patients. MTB GENE-XPERT, gram stain, bacterial culture sensitivity, India Ink stain, Cryptococcal antigen and JC virus PCR was sent from CSF sample as and when clinically indicated. CEMRI Brain was done for most of the patients as and when clinically indicated after patient's consent.

Case Definition:
Tuberculosis [6]
Patients with TBM were categorized as definite TBM (acid-fast bacilli seen on cerebrospinal fluid (CSF) microscopy, positive culture of Mycobacterium tuberculosis in CSF, or positive polymerase chain reaction (PCR) of M. tuberculosis in CSF), probable TBM (diagnostic score ≥12), and possible TBM (diagnostic score 6 - 11) according to the uniform case definition.

Diagnostic Criteria Score
Clinical criteria (maximal category score = 6)
Symptom duration > 5 days (4)
Systemic symptoms suggestive of TB (2)
Focal neurological deficit (1)
Cranial nerve palsy (1)
Altered consciousness (1)

CSF criteria (maximal category score = 4)
Clear appearance (1)
Cells: 10-500 /mm^3 (1)
Lymphocytic predominance (>50%) (1)
Protein concentration > 1 g/L (1)
CSF to plasma glucose ratio < 50% and/or CSF glucose concentration < 40 mg/dl (1)

Cerebral imaging criteria (maximal category score = 6)
Hydrocephalus (CT and/or MRI) (1)
Basal meningeal enhancement (CT and/or MRI) (2)
Tuberculoma (CT and/or MRI) (2)
Infarct (CT and/or MRI) (1)
Pre-contrast basal hyper density (CT) (2)

Evidence of TB elsewhere (maximal category score = 4)
Chest radiograph suggestive of active TB (2)
Chest radiograph suggestive of miliary TB (4)
Radiological evidence of TB outside the CNS (2)
Extra neural Mycobacterium tuberculosis confirmation (4)

Toxoplasmosis [7,8]
1) Positive IgG antibody test for T. gondii in serum
2) Typical imaging features – multiple ring-enhancing lesions with a predilection for the basal ganglia, thalami, and corticomedullary junction
3) Compatible clinical findings with correlating imaging findings
4) Response to treatment at the end of 7 to 14 days-
a. Clinical- improved cognition, reduction of focal neurological deficit
b. Imaging- reduction in size, number and no new lesions
5) Exclusion of other etiologies
6) Biopsy if indicated

Cryptococcal meningitis [7]
1) Cryptococci seen on India Ink stain in CSF
2) Cryptococcal antigen in CSF
3) CSF culture for Cryptococcus

Progressive multifocal leukoencephalopathy (PML) [7]
1) Typical clinical features
2) Typical imaging features – multifocal demyelinating lesions in white matter
3) Other etiologies ruled out.

Outcome:
All the patients were treated appropriately as per standard of care. Discharged patients were followed up in the outpatient department. Outcome of the disease was recorded as 90-day mortality rate.

RESULTS

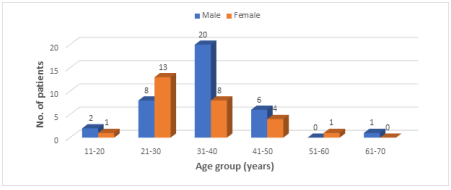
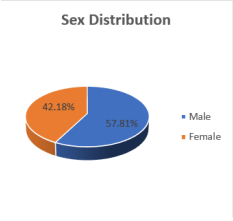


Fig. 1: Distribution of male and female patients as per age groups



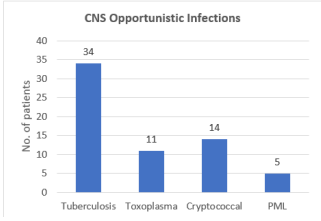


Fig.2: Pie diagram showing sex distribution
Fig.3: Frequency of CNS opportunistic infections

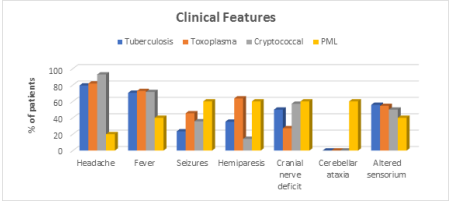


Fig. 4: Clinical features of CNS opportunistic infections

Table 1: CSF Parameters of Opportunistic Infections

OPPORTUNISTIC INFECTION CSF PARAMETERS	Tuberculosis (n=34)	Toxoplasma (n=11)	Cryptococcal (n=14)	PML (n=5)
Protein (mg%)	M=90.94	M=52.27	M=73.92	M=34.2
	R=68-156	R=30-105	R=28-196	R=28-40
Sugar (mg%)	M=39.12	M=51.28	M=56	M=64.2
	R=26-58	R=28-82	R=27-93	R=49-97
Cells (per mm^3)	M=72.67	M=21.72	M=28.71	M=3.8
	R=12-226	R=6-34	R=1-110	R=1-10
ADA (U/L)	M=18.5	M=5	M=6	M=5
	R=3-38	R=2-8	R=3-14	R=1-8
AFB smear	0	0	0	0

MTB GENE-XPERT	1	0	0	0
India Ink stain	0	0	9	0
Cryptococcal antigen	0	0	14	0
JC virus PCR	0	0	0	1

M = Mean, R = Range

Table 2: Brain Imaging features

OPPORTUNISTIC INFECTION IMAGING FEATURES	Tuberculosis (n=34)	Toxoplasma (n=11)	Cryptococcal (n=14)	PML (n=5)
Granulomas	8	10	0	0
Basal Exudate	1	0	0	0
Hydrocephalus	6	0	2	0
Infarcts	11	0	2	0
Cerebral atrophy	5	1	5	0
Meningeal enhancement	13	1	3	0
Demyelination	0	0	0	5
Normal study	6	1	4	0

Table 3: Mortality in opportunistic infections

OPPORTUNISTIC INFECTION	MORTALITY
Tuberculosis (n=31)	6
Toxoplasma (n=11)	2
Cryptococcal (n=13)	5
PML (n=5)	2

Nine patients were readmitted for varied indications while four patients (three tuberculous meningitis and one cryptococcal meningitis) were lost to follow up after discharge. Mean CD4 count of the 15 patients who expired was 46.33 ± 30 cells per mm^3.

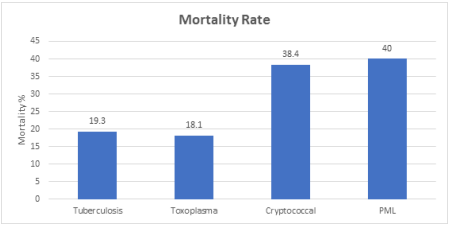


Fig. 5: Mortality Rate of opportunistic infections

DISCUSSION

Fig 1 shows distribution of all HIV positive cases as per age groups. Mean age 32.89 ± 9.21 years (range 18-61 years) and median age of our patients was 32.5 years. Subjects in our study were 42.18 % males and 57.81 % females. Mean CD4 count of our study population was 105.93 ± 77.17 cells per mm^3.

Tuberculosis

In our study, 34 patients had central nervous system tuberculosis out of which 31 patients had tubercular meningitis; five of these patients also had tuberculoma(s) in brain. Three patients only had tuberculoma(s) in brain with no CSF or clinical evidence of tubercular meningitis. Seven out of 34 patients had disseminated tuberculosis with three patients having pulmonary tuberculosis and four patients having pulmonary as well as abdominal tuberculosis in addition to central nervous system tuberculosis. Satishchandra P. et al [9] reported 29 patients of neurotuberculosis in 80 patients of HIV with opportunistic infections. Of the 24 cases, 16 were tubercular meningitis and eight were tuberculomas. Wadia et al [10] in a series of 457 patients found 11.87% cases of neurotuberculosis. Mean time interval from onset of symptoms to admission was 44.23 ± 32.43 days. This was 27.85 days as reported by Katrak S.M. et al [11] and 60 days as per study by Satishchandra P. et al [9]. Clinical data of our patients showed headache in 79.4% followed by fever in 70.5% patients to be the most common symptoms. Presence of hemiparesis (35.2%) was associated with poor outcome in our study {x^2(1, N=31) = 4.37, p=.03}. Mean CD4 count of patients with CNS tuberculosis in our study was 143.5 ± 81.58 per mm^3. CSF examination was done in all our patients. Mean protein level was 90.94 ± 22.02 mg% and mean cell count was 72.67 ± 59.01 per mm^3. Observations made by Katrak S.M. et al [11] and Dubé et al [12] were close to ours. However, Satishchandra P. et al [9] observed higher mean protein levels. Neuroimaging (CT scan) was done in all these patients and MRI was performed whenever clinically required. Ring enhancing lesion were found in 23.52%, basal exudates in 2.94%, hydrocephalus in 17.64%, arterial infarcts in 32.35% cases, and meningeal contrast enhancement in 38.23% cases. Some of these findings differ from other studies. Basal exudates (33.3%), hydrocephalus (5.5%), infarcts (48.9%) granuloma (33.3%) were observed by Katrak S.M. et al [11] Satishchandra P. et al [9] found infarcts in 38.9% and basal exudates in 9.09% cases. Otherwise, their observation was like ours. Yechoor et al [13] found hydrocephalus in 38%, Dubé et al [12] found 20% cases of hydrocephalus and granuloma in 60%. Thus, there was variability in the results in various studies. 6/31 (19.3%) cases expired during in-patient treatment in the group. All six patients had tubercular meningitis. None of the three patients with only brain tuberculoma(s) expired. Four out of seven patients with disseminated tuberculosis expired while one was lost to follow up. In total, three out of 34 patients with CNS tuberculosis were discharged against medical advice and were lost to follow up, so they were not considered while calculation for mortality assessment. Thus, when HIV was co-existent with disseminated tuberculosis patients had very poor prognosis {X^2(1, N=31) = 10.66, p=.001}.

Toxoplasmosis

In our study, 11/64 (17.18%) cases of CNS toxoplasmosis were found. Higher incidence was observed by Indian authors like Satishchandra P. et al [9] (16.25%), Chaddha et al [14] (30.43%) while between 1-8.9% by Wadia et al [10]. Our observations were within the wide range observed by these authors. Mean interval between symptom to admission was 21.54 ± 16.34 days. Headache (81.81%) was the most common symptom in our series followed by fever (72.72%). Satishchandra P. et al [9] in 13 patients found convulsion, focal neurological deficit as main neurological symptoms. Mean CD4 count in our study was 57.18 ± 29.72 per mm^3 in patients with CNS toxoplasmosis. Chaddha et al [14] and Satishchandra P. et al [9] observed CD4 count < 100 in their patients. CSF examination was done in all the patients. Mean CSF protein levels was 52.27 ± 22.90 mg%, cells 21.72 ± 9.88 per mm^3 with lymphocytic predominance. Satishchandra P. et al [9] had similar observations. In their study, CSF cell count was < 50/cmm and protein was between 100-200 mg%. Serological tests were done in all our patients; IgM was positive in 2, IgG was positive in 11, both positive in 2 patients.

CT scan was done in all patients. 10/11 (90.90%) cases had granuloma. Bilateral granuloma in four patients, unilateral in six patients. Granuloma(s) were found in three patients in basal ganglia only, in two patients only in thalamus while two patients had granuloma(s) in both thalamus and basal ganglia. Frontal + parietal (2), frontal only (1), parietal (1) and cerebellum (1) were the other site wise occurrence of granulomas. Single granuloma was seen in six patients, 2-4 granuloma in three patients and five or more granulomas in two patients. All granulomas were ring enhancing lesion. No case of hydrocephalus, basal exudates or infarct was found. Chaddha et al [14] amongst 11 cases found single granuloma in five patients and multiple granulomas in six patients. Satishchandra P. et al [9] in 13 patients found contrast enhancing granulomas in eight patients with basal ganglia and

frontoparietal cortex as a common site. Multiple lesions were found in one patient. There was wide variability in observations made by various authors. 2/11 (18.18%) patients died in our study. Both patients with ≥ 5 granulomas expired. Both patients had very low CD4 counts (<20). These indicate the poor prognostic factors in patients with toxoplasma, however, the data is too small to conclusively comment upon it. Other patients responded to standard anti-toxoplasma treatment. Almost complete remission of ring enhancing lesion was seen on follow up CT scan done after 3-4 weeks of treatment in the surviving patients. Satishchandra P. et al [9] reported 8/13 deaths. Postmortem was done in all those, which showed toxoplasma meningoencephalitis or disseminated toxoplasmosis. Chaddha et al [14] reported 1/11 death.

Cryptococcal Meningitis

In our study, we came across 14 (21.87%) cases where cryptococcal meningitis was present. Reports from Indian and western authors differ in range. Cryptococcal meningitis is dominant/most common opportunistic infection in western countries. Satishchandra P. et al [9] 46.30%, Wadia et al [10] 11.87%, are some Indian authors with wide range of observations. Mean duration of symptoms prior to admission was 32.35 ± 23.87 days. Headache (92.85%) followed by fever (71.42%) were the most common symptoms in our patients. Severe headache with or without fever was the most common symptom in 24 cases reported by Satishchandra P. et al [9]. Similar findings were noted by Jorge et al [15] with headache, fever and altered sensorium in descending order of frequency.

Mean CD4 count was 77.07 ± 51.15 per mm^3 in patients with cryptococcal meningitis. CSF examination was done in all patients. Mean CSF protein level was 73.92 ± 41.54 mg%. Mean cell count was 28.71 ± 28.46 per mm^3. All CSF samples were positive for Cryptococcus antigen. India Ink preparation was positive in 9/14 (64.28%) patients. Satishchandra P. et al [9] found 86.1% India Ink positive cases. Cryptococcal antigen was detected in 35/36 patients. CT scan was done in all cases while MRI brain was done when clinically indicated. None showed basal exudates. Hydrocephalus and infarcts were present in 14.28% patients each. Brain imaging was normal in four (28.57%) cases. CT scan was normal in 59.4% cases, mild hydrocephalus in 25% cases, diffuse cerebral edema in 9.4% cases were the observations made by Satishchandra P. et al [9]. All patients in our study received 2 weeks of 0.7 mg/kg amphotericin B + 800 mg fluconazole daily, followed by maintenance therapy with 200 mg single daily dose of fluconazole. 5/13 (38.4%) patients expired while one was lost to follow up. Mortality was 51% in the study conducted by Satishchandra P. et al [9] where at least one month follow up was done.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy was found in 5/64 (7.81%) of our cases. Chaddha et al [14] (4.35%) reported incidence of Progressive multifocal leukoencephalopathy. Mean duration of symptoms prior to hospitalization was 36 ± 17.10 days. Seizures (60%), hemiparesis (60%) and cranial nerve deficit (60%) was noted in three patients each. Sheila Gillespie et al [16] in study of 79 cases reported motor function abnormalities (67%), altered mentation (66%), hemiparesis (39%) as prominent clinical features. Number of patients in our study was too small to draw any conclusion. Mean CD4 count in our patients with progressive multifocal leukoencephalopathy was 38.6 ± 32.68 per mm^3 which suggests significant immunosuppression. CSF examination was done in all our patients. Mean CSF protein level was 34.2 ± 7.08 mg% and mean cell count was 3.8 ± 3.63 per mm^3. CSF for JC virus PCR was positive in one patient and negative in one patient. It could not be done in rest of the three patients due to non-affordability. CT scan followed by MRI brain was done in all cases. CT scan was normal in three cases while it showed non-enhancing white matter hypodensities in two cases. In all the patients, MRI showed white matter lesions which were hyperintense on T_2W images. Lesions were bilateral in two cases. Cerebellar peduncles were involved in two cases. Contrast enhancement, edema, atrophy was not seen in any of the cases. Diffusion study was carried out in all cases. No infarcts or space occupying lesions were observed. Our observations favor the typical picture of Progressive multifocal leukoencephalopathy well described by many authors. 2/5 (40%) patients with Progressive multifocal leukoencephalopathy expired in our study.

CONCLUSIONS

- Predominantly young adults between age group of 21 to 40 years are affected by central nervous system opportunistic infections in HIV patients.
- Tuberculosis is the most common central nervous system opportunistic infection in HIV patients in our study.
- Disseminated tuberculosis in people living with HIV/AIDS have poor mortality outcome when compared to patients with CNS tuberculosis.
- Yield of acid-fast bacilli (AFB) smear in CSF sample is very low, hence polymerase chain reaction (PCR) should be considered in doubtful cases. Sensitivity of PCR is also not very high, hence final decision regarding diagnosis should be made clinically looking at the overall clinical picture and response to treatment must be tailored.
- CNS toxoplasma and cryptococcal meningitis have similar incidence but prognosis differs. Toxoplasma has favorable prognosis, while cryptococcal meningitis has adverse prognosis.
- India Ink preparation for Cryptococcus has low sensitivity hence, CSF for cryptococcal antigen test is advisable in all patients suspected with cryptococcal meningitis.
- Patients with progressive multifocal leukoencephalopathy had the worst mortality rate in our study.
- Low CD4 count (< 50 cells per mm^3) in the presence of any central nervous system opportunistic infection in HIV patients is associated with high mortality rate. {$X^2(1, N=60) = 26.29, p< .00001$}

Limitations of our study

1) In our study, we did not find any case of neurosyphilis, cytomegalovirus infection, HTLV-1 infection, Herpes encephalitis, Epstein Barr Virus encephalitis or primary CNS lymphoma.
2) Our study conclusions were limited by small sample size.

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