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Study of CNS Infections in HIV Positive Patients

Hemant Mahajan[1*], Deepak Bhutkar[2], Naresh Gill[3], Maya Padvi[4]

[1]Assistant Professor, RCSM GMC Kolhapur, Maharashtra, INDIA.

[2, 3, 4] Junior Resident, TN Medical College, Mumbai, Maharashtra, INDIA.

[*]Corresponding Address:

hemant.mahajan.84@gmail.com

Research Article

Abstract: **Objective:** 1) To study proportions of various central nervous system infections in HIV positive patients. 2) To study the correlation between central nervous systems infections and CD4 counts. **Material and Methods:** A cross sectional observational study was conducted at TN Medical College Mumbai. Total 50 HIV positive patients having neurological manifestations were included in this study. The information was gathered by personal interview using semi-structured proforma. **Results:** shows majority of the patients 37 (74%) were males and 33 (66%) of patients were from 30 to 49 years of age group. Maximum patients had TB meningitis followed by tuberculoma. Only 10 (20%) of patients had CD4 counts more than 200 of which 9 (90%) were males. Patients' on anti-retroviral therapy had more mean CD4 count. Patients diagnosed with Toxoplasmosis and Neurocysticercosis had minimum CD-4 cell count of 50 to 100. 42 (84%) HIV patients with neurological complication had other opportunistic infections and most of these patients had CD4 count less than 200. Total42 (84%) of 50 patients had associated opportunistic infections of which 17 (40.5%) had pulmonary tuberculosis, 13(30.9%) had abdominal tuberculosis. Of these 42 patients having associated opportunistic infection 26 (61.9%) patients were not taking ART. Opportunistic infections were more common in patient's not taking ART. **Summary and Conclusion:** In our study it was found that opportunistic infections were the most common cause of neurological involvement in HIV infected patients. The mean CD4 count was significantly low in all neurological manifestations suggesting severe immunosuppression. Thus neurological manifestations can serve as a good predictor of the advanced HIV infection. Hence CD4 count can serve as an indicator for initiation of chemoprophylaxis of certain opportunistic infections.

Keywords*:* HIV, CNS infections, CD4 count, Opportunistic infections

Introduction:

In 1981 physicians became aware of frequent occurrence of otherwise rare opportunistic infections and neoplasm notably Pneumocystis Carini and Kaposi's sarcoma in otherwise healthy homosexual males. Study of these patients lead to recognize new viral disease AIDS (Acquired Immune Deficiency Syndrome). Human immune deficiency virus infection characterized by acquired and usually profound decreased in immunity in our body (there is reduction in CD4 cell count). In span of 20 years HIV and AIDS have spread worldwide. World Health Organization estimates approximately 34,000,000 adults are infected with AIDS and about 2 to 3.6 million are in India.[1] In India HIV infection mainly occurs by heterosexual sex along with IV drug addicts, iatrogenic and homosexual sex. Of all patients of HIV infection with acquired Immune deficiency syndrome 40% to 60% will develop neurological symptoms.[2],[3] Neurological manifestations of HIV infection and AIDS are being recognized with increased frequency that parallels the increasing number of AIDS case. True prevalence of HIV related neurological complications is not available due to inadequate medical facilities, social stigma and ignorance leading to under diagnosis. In advanced disease involvement of central nervous system is frequent problem and may be due to HIV infection itself or may be caused by opportunistic pathogens or malignancies. Presentations of these disorders are overlapping and nonspecific. The optimal time to initiate antiretroviral therapy in CNS infections is not known.[4] Prompt diagnosis of potentially treatable CNS infections is crucial, but is often limited by lack of diagnostic tests of sufficient sensitivity and specificity, particularly in developing countries like in India. CNS tuberculosis followed by Cryptococcosis and Toxoplasmosis are major neuropathology reflecting endemic and manifesting clinically by reactivation of latent infection. Viral infections appear frequently while HIV associated neoplasm; HIV encephalitis and AIDS dementia complex, are infrequent. Peripheral neuropathy is due to vasculitis, sometimes due to drug toxicities and spinal cord involvement is also rare. Central nervous system infections are the third most common cause of morbidity and second commonest cause of mortality in HIV infected patients. In developing country like India majority of CNS opportunistic infections occur and are often presenting feature of HIV infection and cause major burden on health care sector hence to introduce preventive measures has prime importance. In this study the evaluation of neurological manifestations in HIV infected patients was done. The primary focus was to help in early detection and prompt treatment of these infections to reduce significantly the morbidity and mortality in HIV infected patients.

Materials and Method:

The study was conducted at Topiwala National Medical College, Mumbai a tertiary care hospital. This hospital is situated at a Southern suburb of Mumbai which comes under the jurisdiction of Municipal Corporation of Greater Mumbai. Daily on an average 250 to 300 patients visit to Medicine Out Patient Department. By taking into consideration inclusion and exclusion criteria 50 HIV (human immunodeficiency virus) positive patients with neurological symptoms admitted to the medical wards were selected for present study. Pregnant patients were excluded from the study. A valid consent was taken before starting the study. This cross sectional observational study was carried out during the period of October 2010 to June 2011.

Semi structured interview schedule was constructed relevant to the study .Voluntary consent form was prepared in English, Hindi and Marathi. For this study prior approval from the institutional Ethics Committee was taken.

The presence of the HIV infection was confirmed as per the National AIDS Control Organization guidelines. Through history was taken for demographic factors, various neurological complaints viz; headache, altered sensorium, seizures, imbalance, forgetfulness, tingling numbness, weakness in lower limbs, focal neurological deficit. History regarding ART (Anti-retroviral therapy) status was also evaluated. Detailed neurological examination was done for higher functions including Minimental scale examination, motor system, sensory system and cerebellum examination. From clinical history and clinical examination clinical diagnosis was done and relevant biochemical, radiological (CT, MRI brain), electro-diagnostic (Electro-Myography) investigations were carried out. CSF (Cerebro-spinal fluid) examination done for Cytology, Proteins, Sugars, Gram/ Ziehl Neelson staining and India Ink preparation.

IgG Anti-toxoplasma antibody titre: Toxoplasmosis infection was diagnosed on serology study.

For acute infection-

IgM titre < 1: Negative; IgM titre 1 -2; Equivocal; IgM titre > 2 : Positive.

For chronic infection-

IgG titre < 1: Negative, IgG titre 1 -2 : Equivocal; IgG titre > 2 : Positive.

The immune status was assessed on the basis of the CD4+ cell count using a fluorescent activated cell sorter count in all patients in the study. HIV viral load could not be determined due to financial restrains.

The collected data was numerically coded and entered in Microsoft Excel 2007 and then transferred to SPSS version 15.0 Added data was analyzed with appropriate test like Chi-square test to see the association with p value 0.05 considered as significant.

Results:

TABLE 1 show; majority of the patients (74%) were males and 66% of patients were from 30 to 49 years of age group. TABLE 2 shows; maximum patients had TB meningitis followed by tuberculoma. TABLE 3 shows all patients had fever at the time of admission followed by headache in most of the patients, whereas lower limb weakness and imbalance were present only in Toxoplasmosis patients. Altered sensorium and amnesia were most common in Tuberculous meningitis patients. TABLE 4 shows, only 10 (20%) of patients had CD count more than 200 of which 90% were males. TABLE 5 and 6 shows; 43 (86%) patients were aware of their HIV positive status, 24 (48%) patient's were on anti-retroviral therapy and had more mean CD4 count. TABLE 7 shows; patients diagnosed with Toxoplasmosis and Neurocysticercosis had minimum CD-4 cell count of 50 to 100. TABLE 8 shows; most of the patients diagnosed with Cryptococcal meningitis were taking ART; whereas none of the patients having neurocysticercosis were taking ART. TABLE 9 shows; most (84%) of the HIV patients with neurological complication had other opportunistic infections and most of them had CD4 count less than 200. TABLE 10 shows 42 (84%) patients had associated opportunistic infections of which 17 had pulmonary tuberculosis, 13 had abdominal tuberculosis. Of these 42 patients having associated opportunistic infection 26 patients were not taking ART. Opportunistic infections were more common in patient's not taking ART.

Table 1: Distribution of patients' according to age and sex

Age	Male	Female	Total
< 20	2 (4%)	2 (4%)	4 (8%)
20 – 29	5 (10%)	2 (4%)	7 (14%)
30 – 39	13 (26%)	5 (10%)	18 (36%)
40 – 49	12 (24%)	3(6%)	15(30%)
50 – 59	4 (8%)	1(2%)	5(10%)
60 – 70	1(2%)	0 (0%)	1(2%)
Total	37 (74%)	13(26%)	50 (100%)

Table 2: Distribution of patients' according to diagnosis

Diagnosis	n - 50	Male	Female
Cryptococcal meningitis	9 (18%)	6 (66.7%)	3(33.3%)
Neurocysticercosis	1 (2%)	0 (0%)	1(100%)
TB Meningitis	19 (38%)	12 (63.2%)	7 (36.7%)
Toxoplamosis	8 (16%)	7 (87.5%)	1 (12.5%)
Tuberculoma	12 (24%)	11(91.7%)	1(8.3%)
Cryptococcal meningitis with TB meningitis	1(2%)	1(100%)	0 (0%)

Table 3: Distribution of symptoms in various neurological conditions

Symptoms		TB Meningitis (n-19)	Cryptococcal meningitis (n-9)	Tuberculom (n-12)	Neurocysti-cercosis (n-1)	Toxoplamosis (n-8)
Headache	n	18	9	10	1	6
	%	94.73	100	83.33	100	75
Fever	n	19	9	12	1	8
	%	100	100	100	100	100
Altered sensorium	n	15	1	6	0	3
	%	78.95	11.11	50	0	37.5
Seizure	n	13	2	5	1	6
	%	68.42	22.22	41.66	100	75
Hemiplegia	n	2	1	7	0	1
	%	10.52	11.11	58.33	0	12.5
Lower limb weakness	n	0	0	0	0	2
	%	0	0	0	0	25
Imbalance	n	0	0	0	0	1
	%	0	0	0	0	12.5
Amnesia	n	11	1	1	0	1
	%	57.89	11.11	8.33	0	12.5

Table 4: Distribution of patients according to CD4 count

CD 4 count	Sex		Total
	Male	Female	
< 200	28 (75%)	12 (25%)	40 (100%)
> 200	9 (90 %)	1 (10%)	10 (100%)
Chi- square value = 0.786; df- 1; p - 0.375			
Non-significant difference			

Table 5: Distribution of patients according to awareness of HIV positive status

Awareness of HIV positive status	Frequency
Yes	43 (86%)
No	7 (14%)

Table 6: Distribution of patients' according to ART status

ART Status	Frequency	Mean CD4 Count
Yes	24 (48%)	131.1
No	26 (52%)	85.11

Table 7: Average CD4 count in different neurological conditions

Neurological Manifestation in HIV patients'	CD - 4 count cells/µl
TB meningitis	100 -250
Tuberculoma	150 - 250
Toxoplasmosis	50 - 100
Cryptococcal meningitis	100 - 200
Neurocystecercosis	50 - 100

Table 8: Distribution of patients' according to ART status

Neurological Manifestations	Total	No ART (26)	On ART (24)
TB meningitis	19	11 (57.9%)	8 (32.1%)
Tuberculoma	12	8 (66.7%)	4 (33.3%)
Toxoplasmosis	08	2 (25%)	6 (75%)
Cryptococcal meningitis	09	3 (33.3%)	6 (66.7%)
Neurocystecercosis	01	1(100%)	0 (0%)
Cryptococcal meningitis with TB meningitis	01	1(100%)	0 (0%)
Total	50	26 (52%)	24 (48%)

Table 9: Distribution of patients according to associated opportunistic infection

Associated Opportunistic Infections	Frequency	CD4 count < 200	CD4 count > 200
Abdominal TB	13 (26%)	10 (76.9%)	3 (23.1%)
Herpes Zoster	6 (12%)	5 (83.3%)	1 (16.7%)
Oral Candidiasis	6 (12%)	4 (66.7%)	2 (33.3%)
Pulmonary TB	17 (34%)	13 (76.5%)	4 (23.5%)
Total	42 (84%)	32 (76.2%)	10 (23.8%)

Table 10: Association of associated opportunistic infection and ART status

Associated opportunistic infection		ART		Total
		Yes	No	
Abdominal TB	n	4	9	13
	%	30.7	69.3	100
Herpes Zoster	n	2	4	6
	%	33.3	66.7	100
Oral Candidiasis	n	3	3	6
	%	50	50	100
Pulmonary TB	n	7	10	17
	%	41.2	58.8	100
Total	n	16	26	42
	%	38.1	61.9	100

Discussion:

This cross sectional observational study was carried out in Topiwala national Medical College, Mumbai from October 2010 to June 2011.

In this study 50 HIV positive patients with neurological involvement were involved, of which 74% patients were males. The male: female ratio being 2.84: 1. Gongora Rivera F et al 2000 [6] in their study found 89.3% males and 10.7% Female patients. Attili Venkata Satya Gulati A kumar et al in 2006[5] had found that males were higher in number than females. The male: female ratio was 3.7: 1. Satishchandra P et al 2000 [7] in study of 100 patients found 95% males and 5% females. Jowi Jo et al 2007[9] have 86 (57.3%) Males and females 64 (42.7%) with M: F ratio = 1.3:1 in their study. The number of male patients was more than females probably due to high risk behaviors of males and heterogeneous route of transmission of HIV.

Maximum number of patients were in the age group of 30- 49 i.e. 66% (n - 33).Mean age of all patients was 34.33 $\pm$ 2.3 years. Least number of patients were in the age group of 60-70 i.e. 2% (n-1). Satishchandra P et al [7] studied 100 patients for the pattern of neurological manifestations. In their study, 37 patients had mean age of 31.6$\pm$ 9.4. Vijay D Teja et al 2005[8] studied 414 HIV positive patients, they found that maximum number of patients were in the age group of 30-40 with mean age of 36.6 years. Higher percentage were present in this group which can be explained by increased sexual activity in this age group as HIV is mainly transmitted by the sexual route.

In our study 43 (86%) patients were aware of their HIV positive status at the time of admission for neurological symptoms, whereas 7 (14%) were diagnosed on admission i.e. their first presentation was a neurological involvement. Vijay D Teja et al[8] found that only 9.25% of their patients were aware of their HIV positive status at the time of admission for neurological involvement.

We observed that all patients had neurological involvement due to an infectious aetiology. Similar study carried out by Satishchandra P et al[7] in 2000 found that 80% of the total patients had infectious cause for neurological manifestations and remaining 20% had non-infectious cause for neurological manifestations.

In our study 38% of patients had Tuberculous meningitis, 24% patients had Tuberculoma, 18% patients had Cryptococcal meningitis and 8% had Toxoplasmosis, 2% patients had Neurocysticercosis and 2% patients had both Tuberculous meningitis and Cryptococcal meningitis. Diagnosis of Cryptococcal meningitis was based on presence of cryptococcal antigen on CSF analysis and that of Tuberculous meningitis was based on high CSF ADA level. Similar study done by Attili Venkata Satya Gulati A Kumar et al 2006[5] on 57 patients on ART having neurological manifestations found that 43% patents had Tuberculous meningitis, 28% patients had Cryptococcal meningitis, 8.7% patients had Toxoplasmosis, 5.26% patients had PML. Jowi et al[9] in 2007 had studied 150 HIV patients with neurological involvement and in that Cryptococcal meningitis was seen in 33 (22%) patients, viral encephalitis was seen in 28 (18.7%) patients, Cerebral Toxoplasmosis was seen in 19 (12.7%) patients, Stroke (vascular) in 19 (12.7%) patients and Tuberculous meningitis in 16 (10.7%) patients. The other rare neurological manifestations included peripheral neuropathy, HIV associated dementia, myelopathy and myopathy amongst others.

In our study we had only 24 (48%) patients were taking ART. Amongst the patients who were on ART, 8 had Tuberculous meningitis, 6 patients had toxoplasmosis, 6 patients had Cryptococcal meningitis and 4 patients had Tuberculoma. Some of these patients had opportunistic infections inspite of being on ART. This could possibly result from IRIS (Immune Reconstitution Inflammatory Response Syndrome), virological or immunological failure. With the invent of ART the incidence of opportunistic infections decreased remarkably in the West; however in countries like India where the prevalence of opportunistic infections is very high because of poor compliance of patients with ART due to cost, side effects and unavailability of ART.

In our study the mean CD4 count was calculated in all patents with various neurological manifestations. Patients with Tuberculous meningitis had mean CD4 count of 138.68$\pm$ 35.61 cells/pt, patients with Cryptococcal meningitis had mean CD4 count of 81.23$\pm$ 18.2 cells/pt, patients with Toxoplasmosis had mean CD 4 count of 83.7$\pm$ 17.4 cells/pt. Jowi et al[9] in 2007 had studied 150 HIV patients with neurological involvement; CD4 count was available in 72 patients. Patients with encephalitis had mean CD4 count of 82 , patients with Cerebral Toxoplasmosis had mean CD4+ count of 59 cells, patients with focal neurological deficit had mean CD4+ count of 120 cells, Tuberculous meningitis patients had mean CD4+ count of 67 cells. Thus in our study mean CD4+ count was significantly low in all neurological manifestations suggesting immunosuppression. This is consistent with the study of relationship between several neurological complications and CD4+ count by Gochitashvili N et al in 2005[10].

In our study mean CD4+ count for the patients who were not on ART was 85.11 In the study done by Vijay D Teja et al[8] in 2005, CD4+ cell count was available in 123 patients out of 411, mean CD4 + cell count was < 200 in majority of patients. This indicates the 4th stage of WHO clinical staging system. Clinical presentation of these patients also indicated severe stage of disease. In our study only 10 (20%) patients were had CD4 count more than 201 out of which 90% were males.

In our study there were 19 patients of Tuberculous meningitis most of them presented with fever and headache. Altered sensorium and focal neurological deficit were also present in few patients. In a study conducted by Attili Suresh Venkata Satya et al[5] in 2006 found that 87.5% patients of Tuberculous Meningitis presented with headache, 75% of patients had fever as the presenting symptom. Out of 19 patients of Tuberculous meningitis 17 patients had CD4+ count less than 200 cells/ml. 12 of 19 Tuberculous meningitis patients were aware of their HIV positive status, 11 patients were not on ART and 14 patients had an associated opportunistic infection.

In our study majority of patients of Tuberculous meningitis 73% (14) patients had cortico-cerebral atrophy with basal exudates. In a study by Whiteman et al[11] central nervous system TB patients 36% patients had basal exudates, 44% patients had ring enhancing granuloma and remaining had hydrocephalus and infarct in CT brain.

Majority of Toxoplasmosis patients (87.5%) in our study presented with headache, 5 (62.5%) patients had seizure episode at presenting symptom and 3 (37.5%) had focal neurological deficit. 6 (75%) of 8 toxoplasmosis patients were unaware of their HIV positive status, 75% patients were on ART and 75% patients had associated opportunistic infection. Most of the patients had CD4 count in the range of 50-100. In a study conducted by Attili Suresh Venkata Satya et al[5] in 2006 found that all toxoplasmosis patients had focal neurological deficit as a presenting complaint.

Of these12 patients of Tuberculoma all had fever and 10 (83.3%) had headache. Altered sensorium and focal neurological deficit were also present in few patients. 66.7% of total tuberculoma patients were unaware of their HIV status, only 4

(33.3%) were taking ART and 8 (66.7%) patients had associated opportunistic infection.

Diagnosis of Cryptococcal meningitis was based on CSF study. Out of 9 Cryptococcal meningitis patients 8 (88.9%) presented with headache, 3(33.3%) had seizure, 3 (33.3%) had focal neurological deficit as a presenting symptom. 6 (66.7%) patients were aware of their HIV positive status at the time of admission, 6 (66.7%) were on ART and most of the patients had CD4 count in the range of 150-250. Only one patient of neurocysticercosis was found in our study presenting with fever, headache and seizure. He was unaware of his HIV status with CD4 count in the range of 50-100.

In our study 12 (24%) patients had peripheral neuropathy. Of these 10 (83.3%) were on ART. Higher percentage can be attributed to ART related peripheral neuropathy.

Conclusion and Recommendation:

In our study it was found that opportunistic infections were the most common cause of neurological involvement in HIV infected patients. The mean CD4 count was significantly low in all neurological manifestations suggesting severe immunosuppression. No difference was found with respect to the profile of neurological complications in patients on ART and patients not on ART except for peripheral neuropathy, which occurs significantly in patients on ART. Thus neurological manifestations can serve as a good predictor of the advanced HIV infection. Hence CD4 count can serve as an indicator for initiation of chemoprophylaxis of certain opportunistic infections.

Our study enlightens that the early detection of HIV infection monitoring with CD4 count and initiation of ART might lessen the dreaded central nervous system complications and reduce morbidity and mortality in these patients.

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