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Clinical profile of neurological complications in HIV-reactive patients and their relation with CD4

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ABSTRACT

Background: Neurologic abnormalities have been noted in one-third of patients with AIDS, but at autopsy the nervous system is affected in all of them. **Aim:** To study the clinical profile of neurological complications in HIV reactive patients, study and correlate the neurological complications with CD4 count and study and correlate the radiological findings (on CT brain plain and contrast) of neurological complications in HIV reactive patients, with CD4count. **Methods:** A randomized case study was conducted at Dr. V. M. Government Medical College, Solapur, Maharashtra, India, over a period of 2 years. 50 HIV-infected adult and adolescent patients presenting with neurological manifestations were studied. The diagnosis of HIV was confirmed by 3 HIV ELISA positive reports in symptomatic patients. **Results:** In the present study, 46% of the patients were in the age group of 31-40 years. Males are affected more frequently than females, with a male to female sex ratio of 2.125: 1. Meningitis, intracranial space occupying lesions, and stroke syndromes are the commonest neurological disorders observed in HIV-infected patients. Tuberculosis is the commonest opportunistic infection in retroviral positive patients. Ischemic strokes are a common complication in HIV-infected individuals. Tuberculomas are the most common cause of intracranial space occupying lesions. **Conclusion:** Central nervous system infections, intracranial mass lesions, stroke, and HIV-associated dementia are more common in patients with a CD4+ count less than 200.

Key Words: HIV, AIDS, CD4 count, meningitis, tuberculoma, dementia

INTRODUCTION

The neurological diseases occurring in HIV-infected individuals are either due to primary pathogenic process of HIV infection or secondary to opportunistic infections. Neoplasms directly attributable to HIV occur throughout the course of the infection and may be inflammatory, demyelinating, or degenerative in nature.[1] The diseases which are produced due primarily to pathogenic process of HIV infection include aseptic meningitis, HIV encephalopathy (AIDS dementia complex), various myelopathies, neuropathies and myopathy.[2] Common opportunistic diseases involving the CNS are toxoplasmosis, cryptococcosis, progressive multifocal

leukoencephalopathy, and primary CNS lymphoma.[1]

This study thus evaluates the neurological complications in HIV-reactive patients.

METHODOLOGY

Study Design

A randomized case study was conducted at Dr. V. M. Government Medical College, Solapur, Maharashtra, India, over a period of 2 years; December 2010 to November 2011. 50 HIV-infected adult and adolescent patients (>13 years of age) presenting with neurological manifestations, admitted in above mentioned hospital were studied.

The demographical data like name, age, sex, address, occupation, marital status, socioeconomic status, was collected in all patients. History of high risk behavior, major surgery, and blood transfusion was asked in all patients. The diagnosis of HIV was confirmed by 3 HIV ELISA positive reports in symptomatic patients.

All patients were subjected to detailed general examination and systemic examination with special attention to the central nervous system. All patients were subjected to routine investigations like haemogram, blood biochemistry, and chest X-ray. Other special investigations like CSF analysis, serology, nerve conduction velocity (NCV) studies and neuro-imaging were undertaken as appropriate to individual patient only when mandatory for research project. Absolute CD4+ T-cell count was done in all patients. Lumbar puncture was done for CSF analysis.

The CSF sample was analyzed in the Department of Biochemistry, Pathology and Microbiology at Dr. V. M. Government Medical College, Solapur, Maharashtra, India for sugar and protein, cytology, staining including grams staining, acid-fast bacillus and India ink preparation.

The following reference values were considered abnormal[4]

- CSF sugar
  <40 mg/dL
- CSF protein
  >50 mg/dL
- CSF Leucocyte count >5/mm^3 (Neutrophils ≥ 1/mm^3, Lymphocytes ≥ 5/mm^3)

NCV-EMG studies were carried out in patients presenting with lower motor neuron type of weakness to diagnose and classify type of neuropathy/radiculoneuropathy/myopathy . CT scan of head (with or without contrast injection), was performed in patients, as indicated.

Inclusion criteria

HIV-positive patients showing at least a manifestation of neurological involvement.

Exclusion criteria

HIV-positive patients not showing any manifestation of neurological involvement.

Ethical issues

The study adhered to standards ethics of research involving humans. Ethical clearance was obtained from the Ethical Committee of the institution and written consent of the patient or patient's relatives was also obtained.

Statistical analysis

Data were analysed by chi-square test and Z-test for difference between proportions of two populations were used.

RESULTS

In our study, a total of 50 cases of HIV-reactive patients with neurological manifestations were studied. Out of 50, 26 (52%) patients had meningitis, 8 (16%) patients had intracranial space-occupying lesions, 8 (14%) patients had isolated stroke syndromes, 4 (8%) patients had peripheral neuropathy, 3 (6%) patients had HIV-associated dementia, and 1 (2%) patient had generalized tonic-clonic seizure disorder.

Out of these, the commonest manifestation was meningitis which accounted for 26 cases (52%), followed by 8 (16%) cases of intracranial space-occupying lesions, and 8 (16%) patients of isolated stroke syndromes.

Out of 50 patients studied, 1 (2%) was in the age group of 13-20 years, 14 (28%) were in the age group of 21-30 years, 23

(46%) were in the age group of 31-40 years, 9 (18%) were in the age group of 41-50 years, and 3 (6%) were in the age group of 51-60 years. Thus, maximum numbers of patients were in the age group between 31-40 years. The median age at presentation was 37.5 years.

Tuberculous meningitis was seen in 17 (34%) patients, bacterial meningitis (non-tubercular) was seen in 7 (14%) patients, and cryptococcal meningitis was seen in 2 (4%) patients. Thus, tuberculous meningitis was the commonest type of meningitis observed.

Table 1: Distribution of various neurological complications in HIV-reactive patients

Neurological Complication	Number of Patients	Percentage
Tuberculous Meningitis	17	34
Bacterial Meningitis(Non-Tubercular)	7	14
Cryptococcal Meningitis	2	4
Tuberculomas	7	14
Toxoplasmosis	1	2
CVA	8	16
Peripheral Neuropathy	4	8
HIV-Associated Dementia	3	6
GTCS	1	2
Total	50	100

Table 2: Age-wise distribution of various neurological complications in HIV-reactive patients

Age Group	Number of Patients	Percentage
13-20	01	02
21-30	14	28
31-40	23	46
41-50	09	18
51-60	03	06
Total	50	100

Table 3: Sex-wise distribution of various neurological complications in HIV-reactive patients

Sex	Number of Patients	Percentage
Male	34	68
Female	16	32
Total	50	100

Table 4: Distribution of various types of meningitis in HIV-reactive patients

Type of Meningitis	Number of Patients	Percentage
Tuberculous	17	34
Bacterial (Non- Tubercular)	7	14
Cryptococcal	2	4
Total	26	52

Table 5: Clinical features of various types of meningitis in HIV-reactive patients

Clinical Features	Tuberculous Meningitis		Bacterial Meningitis		Cryptococcal Meningitis	
	Number (17)	%	Number (7)	%	Number(2)	%
Fever	13	76.47	6	85.71	1	50
Headache	10	58.82	2	28.57	2	100
Vomiting	05	29.41	2	28.57	1	50
Seizures	04	23.52	0	0	0	0
Hemiparesis	03	17.64	1	14.28	0	0
Altered Sensorium	09	52.94	4	57.14	0	0
Loss of Consciousness	03	17.64	1	14.28	0	0
Signs of Meningism	12	70.58	7	100	2	100

Table 6: Distribution of intracranial space occupying lesions, stroke syndrome and neuropathy in HIV-reactive patients

Type of Lesion	Number of Patients	Percentage
Tuberculomas	07	87.5
Toxoplasmosis	01	12.5
Stroke syndrome with opportunistic infection	06	12
Stroke syndrome without opportunistic infection	08	16
Type of neuropathy Distal sensory polyneuropathy	01	2
Chronic demyelinating sensory motor polyneuropathy	01	2
Motor neuropathy	01	2
Lumbar radiculopathy	01	2
CD4 count < 200	38	76
CD4 count >200	12	24
CD4 count < 200 (CT abnormality present)	22	61.11
CD4 count < 200 (CT Normal)	14	38.88

Table 7: Distribution of various types of meningitis in different studies on neurological complications in HIV-reactive patients

Type of Meningitis	Bolokadze *et al.*[8]	Singh *et al*.[5]	Present Study
Tuberculous	34%	14.18%	34%
Bacterial	4%	-	14%
Cryptococcal	15%	6.01%	4%

Table 8: Distribution of toxoplasmosis in some previous studies

Toxoplasmosis in following studies	
Hung *et al.*[9]	1.2%
Singh *et al.*[5]	0.72%

In the present study, the number of male patients was 34 (68%) and the number of female patients was 16 (32%).

Out of 17 patients with tuberculous meningitis, fever was present in 13 (76.47%) patients, headache was present in 10 (58.82%) patients, vomiting in 5 (29.41%) patients, seizures in 4 (23.52%) patients, hemiparesis in 3 (17,64%) patients, altered sensorium (inability to understand verbal commands, irrelevant talks, and inappropriate behaviour) in 9 (52.94%) patients, unconsciousness in 3 (17.64%) patients and signs of meningism in 12 (70.58%) patients.

Out of 7 patients with bacterial meningitis (non-tubercular), the commonest findings were the presence of signs of meningism in all 7 (100%), and fever, which was present in 6 (85.71%) patients, followed by altered sensorium seen in 4 (57.14%) patients.

In the 2 patients with cryptococcal meningitis, headache and signs of meningeal irritation were the most consistent findings which were present in both of them.

Out of total 8 patients presenting with intracranial mass lesions, 7 (87.5%) had tuberculomas, while 1 (12.5%) had toxoplasmosis. Thus, tuberculomas accounted for the commonest intracranial mass lesions in the current study.

In the present study, stroke syndromes were present in 14 (28%) patients. Out of 14 patients, 6 (42.85%) patients had ischemic infarcts attributable to underlying CNS opportunistic infection. Out of the 8 (57.14%) patients without an underlying opportunistic infection, 6 (42.85%) patients had thrombotic stroke, 1 (7.14%) patient had intracerebral bleed, and 1 (7.14%) patient had cortical venous thrombosis. Thus, excluding the stroke syndromes secondary to underlying CNS infections, stroke was noted in 8 (16% out of total 50) individuals in the true sense.
In the present study, there were 4 (8%) patients with peripheral neuropathy, 1 (2%) patient had distal sensory polyneuropathy, 1 (2%) patient had chronic demyelinating sensory-motor polyneuropathy, 1 (2%) patient had motor neuropathy and 1 (2%) patient had lumbar radiculopathy.

Out of total 50 patients presenting with neurological manifestations, 38 (76%) had a CD4+ count less than 200 while 12 (24%) had a CD4+ count greater than 200. Thus, most of the HIV-reactive patients presenting with neurological manifestations had a CD4+ count less than 200. The median CD4+ count was 119.

Out of total 46 patients presenting with central nervous system manifestations, CT scan abnormality was present in 30 (65.21%) patients. Out of 46 patients presenting with central nervous system complications, 36 patients had a CD4+ count less than 200. Out of these 36 patients, CT scan abnormality was present in 22 (61.11%) patients, while CT scan was normal in 14(38.88%) patients. Out of 46 patients presenting with central nervous system manifestations, 10 patients had a CD4+ count more than 200. Out of these 10 patients, CT scan abnormality was present in 8 (80%) patients, while CT scan was normal in 2 (20%) patients.

Thus, we found no statistically significant association between CD4+ count and CT scan of head ($p>0.05$).

DISCUSSION

In the present study, out of 50 patients with neurological manifestations, meningitis was present in 26 (52%) patients, intracranial space-occupying lesions were present in 8 (16%) patients, pure stroke syndromes were present in 8 (16%) patients, peripheral neuropathy was present in 4 (8%) patients, HIV-associated dementia was present in 3 (6%) patients and generalized tonic-clonic seizure disorder was present in 1 (2%) patient. The incidence and clinical features of these are discussed below individually.

In this study, the commonest age group of neurological manifestations of HIV disease was 31-40 years comprising of 46% of the total number of patients, and median age was 37.5 years. In our study out of 50 patients, 34 (68%) were males and 16 (32%) were females. The male:female ratio was 2.125:1. In the study conducted by Teja *et al.*, the median age was 36 years, with most

patients in the 30-40 years age group and the male:female ratio was 3.9 :1.[4]

In the study conducted by Singh *et al.*, the peak incidence was seen in the fourth decade of life.[5] Most of the subjects were males, with a male: female ratio of 1.83:1.[6] In the study conducted by Deshpande *et al.*, most of the patients fell in the age group of 15-45 years (76%) and the male:female ratio was 2.94 : 1.[6]

In the present study, 43 (86%) patients fell in the age group of 15-45 years, which is similar to the study conducted by Deshpande *et al*. (p>0.05).[6] Thus, the age group and sex-wise distribution in the present study is similar to the above mentioned previous studies.

In the present study, 26 patients had meningitis, which was the most common neurological manifestation observed, contributing to 52% of the total cohort. Amongst the various types of meningitis, tuberculous meningitis was seen in 17 patients, which accounted for 34% of total neurological complications. The common clinical features observed in the 17 patients with tuberculous meningitis were fever in 13 (76.47%), signs of meningeal irritation in 12 (70.58%), headache in 10 (58.82%), altered sensorium in 9 (52.94%), vomiting in 5 (29.41%), seizures in 4 (23.52%), loss of consciousness in 3 (17.64%) and hemiparesis in 3 (17.64%) patients. Yechoor *et al.* in a similar study found fever (83%) and abnormal mental status (71%) as the most common findings in patients with tuberculous meningitis.[7] The incidence of these findings is similar to that found in our study (p>0.05).[7]

Our findings also correlate well with the study conducted by Bolokadze *et al.*, in which various types of meningitis accounted for 53% of all the neurological complications observed and tuberculous meningitis was the most common cause of neurological affection accounting for 34% of the total cases with neurological complications (p>0.05).[8]

Bacterial meningitis (non-tuberculous) was the second most common cause of meningitis, affecting 7 patients (14% of total patients with neurological complications). The common clinical features observed in these patients were, signs of meningism in all 7 (100%), fever in 6 (85.71%), altered sensorium in 4 (57.14%), headache in 2 (28.57%), vomiting in 2 (28.57%), and hemiparesis in 1 (14.28%) patient. The incidence of bacterial meningitis (non-tuberculous) was higher in our study as compared to study conducted by Bolokadze *et al.*[8]

Cryptococcal meningitis was seen in 2 patients, accounting for 4% of total patients with neurological complications. This occurrence is similar to the study conducted by Singh *et al.* who reported cryptococcal meningitis in 6.01% of their patients with neurological complications (p>0.05).[5] Clinical features noted in these 2 patients were, headache, fever, vomiting, and signs of meningism.[5]

Tuberculomas were the commonest central nervous system mass lesions encountered in the present study, which were diagnosed in 7(14%) out of total 50 patients with neurological complications. There was 1(2%) patient with toxoplasmosis. This correlates with the study conducted by Teja*et al.*, in which 10.71% patients were diagnosed with tuberculomas (p>0.05).[4]

The clinical features noted among the patients with mass lesions were, fever, headache, vomiting, and seizures. In the present study, stroke syndromes were identified in 14 (28%) patients. Out of 14, 5 occurred secondary to an underlying opportunistic infection-induced vasculitis, and 1 occurred secondary to underlying tuberculoma. Thus, strictly speaking, 8 (16% out of 50) patients had a pure stroke syndrome. Out of the 8 patients without an underlying CNS infection or mass lesion, 6 patients had thrombotic stroke, 1 patient had stroke secondary to cortical venous thrombosis and 1 patient had an intracerebral haemorrhage. Hemiparesis was the most common presentation seen in 11 (78.57%) out of 14 patients. The other clinical features noted were seizures, altered sensorium, fever, vomiting, and headache.

Large-scale epidemiologic data on stroke in retroviral positive persons are scarce, particularly in an era of combination antiretroviral therapies, which have prolonged patient survival, but may boost stroke risk.[10] In the study conducted by Thorat *et al.*, stroke was found in 16.6%

patients, which is similar to the incidence of 16% (patients with stroke without an underlying CNS infection) found in present study (*P*>0.05).[11] Connor *et al.* in their study of an autopsy series of patients with AIDS, found a 4% to 29% prevalence of cerebral infarction.[12] Though they could not differentiate cases with cerebral infarction when not associated with non-HIV central nervous system infection, lymphoma, or cardioembolic sources.[12] Thus, occurrence of stroke in HIV-infected individuals is a common finding.

Out of 50 patients in the present study, there were 4(8%) patients with peripheral neuropathy. This is similar to the study of Singh *et al.*, in which peripheral neuropathy was diagnosed in 10.10% of patients presenting with various HIV-related neurological complications (*P*>0.05).[5] 1(2%) patient had distal sensory polyneuropathy, 1(2%) had chronic demyelinating sensory-motor polyneuropathy, 1(2%) had motor neuropathy and 1(2%) had lumbar radiculopathy. Though three patients of these four were already taking anti-retroviral drugs, neuropathy in them could not be attributed to these drugs. Tingling, sensory loss, lower limb distal muscle weakness, backache and imbalance were the clinical features noted.

In the present study, HIV-associated dementia was found to occur in three (6%) patients. All patients showed impaired cognition and out of the three, two patients also had history of seizures. All the three patients were newly diagnosed and not on anti-retroviral drugs. In an Indian study conducted by Teja *et al.*, HIV-associated dementia was seen in 8.03% of all HIV-infected patients presenting with neurological complications.[4] Thus, the incidence of HIV-associated dementia found in our study is similar to that found in the above mentioned study (*P*>0.05).

Overall, out of fifty patients with neurologic manifestations in this study, thirty eight (76%) patients had a CD4+ count less than 200, while twelve (24%) patients had a CD4+ count more than 200. The median CD4+ count was 119. Out of fifty patients in the study, CNS infections were present in thirty four patients. Out of these thirty four, twenty seven (79.41%) patients had a CD4+ count less than 200, and only seven (18.92%) patients had a CD4+ count more than 200. Singh *et al.*, in their study on patients with neurological manifestations in HIV-infected patients, found that 88.23% patients with CNS infections had a CD4+ count of less than 200.[5] This is similar to that found in the present study (*P*>0.05). Teja *et al.*, in a similar study, also found that most HIV-infected patients with neurological complications, had a CD4+ count less than 200 and the median CD4+ count was 89.[4] Most of the patients with HIV-associated dementia in the study conducted by Singh *et al.*, had a CD4+ count less than 200.[5] All three patients with HIV-associated dementia in our study had a CD4+ count less than 100.

Out of the eight patients with stroke syndrome without an underlying opportunistic CNS infection in the present study, six (75%) had a CD4+ count less than 200 and two (25%) had a CD4+ count more than 200. In a study conducted by Oritz *et al.*, 85% HIV-infected patients with stroke had a CD4+ count less than 200.[13] This correlates with our findings (*P*>0.05).

Two patients with peripheral neuropathy had a CD4+ count less than 200 while the other two had CD4+ count above 400. Out of the four patients presenting with peripheral neuropathy, three patients were already taking anti-retroviral drug therapy, but their neuropathy could not be attributed to these drugs. Singh *et al.* in their study had noted that patients with peripheral neuropathy had higher CD4+ counts compared with those presenting with other neurological complications.[4] Thus, we could not establish a significant relationship between the occurrence of peripheral neuropathy and CD4+ count.

In the present study, central nervous system manifestations were seen in forty six patients out of fifty. CT scan was abnormal in thirty (65.21%) patients. As far as cerebral vascular events were concerned, a total of fifty abnormal events were recorded with considerable overlap. The commonest finding was non-enhancing hypodensities, suggestive of infarct seen in sixteen (34.78%) patients, while intracerebral bleed was found in one (2.17%) patient. Thus, we found that

ischemia was a far commoner occurrence compared to intracranial bleed in our study group. Tipping *et al.* also found that occurrence of ischemia was far more common than intracerebral hemorrhage.[14] The other findings noted were, intraparenchymal mass lesions in eight (17.39%) patients, cerebral edema in six (13.04%) patients, atrophy in six (13.04%) patients, hydrocephalus in five (10.87%) patients, meningeal enhancement in four (8.69%) patients, basal exudates in two (4.34%) patients, cortical venous thrombosis in one (2.17%) patient and intracerebral calcification in one (2.17%) patient.

Out of twenty six patients with meningitis, ultrasound scans of thirteen (50%) patients showed abnormalities suggestive of an underlying infection like cerebral edema, vasculitic infarct, meningeal enhancement, hydrocephalus and basal exudates, while thirteen (50%) others had a normal CT scan. Thus we found that CT scan was not a sensitive modality for diagnosis of meningitis though it can guide regarding the complications. Out of thirty six patients with a CD4+ count less than 200 and having central nervous system manifestations, CT scan abnormality was found in twenty two patients, while remaining fourteen had a normal CT scan. Ten patients with central nervous system manifestations in our study had a CD4+ count more than 200, out of which CT scan abnormality was detected in eight, while two patients had a normal scan. We found no statistically significant association between CT scan of the head and CD4+ count (P>0.05).

CONCLUSION

Neurological manifestations of HIV disease are seen more commonly in the younger age group. In the present study, 46% of the patients were in the age group of 31-40 years. Males are affected more frequently than females with a male to female sex ratio of 2.125:1 in the present study. Meningitis, intracranial space occupying lesions, and stroke syndromes are the commonest neurological disorders observed in HIV-infected patients. Central nervous system opportunistic infections account for the most common neurological complications in HIV-infected patients. Tuberculosis is the most common opportunistic infection in HIV-infected patients causing meningitis, intracranial mass lesions and predisposing to stroke. Tuberculous meningitis is the most common meningitis in HIV-infected patients. Ischemic strokes are a common complication in HIV-infected individuals and opportunistic infections also predispose these patients to ischemic strokes. Tuberculomas are the most common cause of intracranial space occupying lesions. Distal sensory polyneuropathy, chronic demyelinating sensory-motor polyneuropathy, motor neuropathy, lumbar radiculopathy, HIV-associated dementia, and generalized tonic-clonic seizure disorder, are less common neurological disorders observed in HIV-infected patients. Central nervous system infections, intracranial mass lesions, stroke, and HIV-associated dementia are more common in patients with a CD4+ count less than 200. There is no significant association between CT scan findings and CD4+ count.

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