Neurological manifestations of HIV infection

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Abstract

Background and Objectives: HIV/AIDS has posed many unprecedented challenges. It causes a wide spectrum of disease manifestations. Approximately 60 % of the AIDS patients have neurological symptoms and 80-90 % have neuropathological abnormality at biopsy. The pattern of neurological complication in HIV infection in India is different from that of western countries. This study was under taken to,

1. Study the neurological manifestations in HIV patients admitted in to VIMS Hospital, Bellary.
2. To note differences with various studies carried out in western countries.

Methods: Patients admitted in VIMS Hospital between December 2010 to June 2012 with symptoms referring to nervous system were screened and confirmed to have HIV-1 and/or HIV-2 infection (seropositive) by ICTC (Trispot test,Trilene test,Dot immunoassay)were enrolled if they met the inclusion criteria.

Results: 58 of the 547 HIV positive patients fulfilled the inclusion criteria and were studied for neurological manifestations (10.6 %). 39 were males and 19 females and mean age of 34 yrs. in males and 29yrs in females. 62.1% were presenting with neurological symptoms and signs for the first time and were diagnosed HIV positive following admission.

Meningitis was the commonest presentation (81.1%), 35(60.3%) patients with tubercular, 9(15.1%) patients with cryptococcal aetiology and 3(5.1%) had bacterial meningitis. Altered sensorium (75.6%), Headache (51.3 %), convulsions (32.4%) and focal neurological deficit (21.6 %) were the commonest presenting neurological symptoms with fever in 89.1 % of all cases. Tubercular involvement in form of meningitis (60.3%) and intracranial space occupying lesion (Tuberculoma) in 2 patients (3.4%) was the single largest etiological agent followed by cryptococcal meningitis 15.1%, 5 patients had CVA, 3 had bacterial meningitis, 2 had myelopathy, 1 had Bell's palsy and 1 patient had Guillain-Barre syndrome. No case of toxoplasmosis or lymphoma was detected.

Interpretation and Conclusion : There is high incidence of neurological manifestations with tuberculosis and Cryptococci being commonest pathogenic agents in course of HIV infections in this study. Simple investigations like CD4 count may provide a clue to the degree of underlying immunosuppression and indicate the need to start ART in HIV/AIDS patients.

Key words: Human immunodeficiency virus, tubercular meningitis, cryptococci.

INTRODUCTION

AIDS was first recognized in the United States in the summer of 1981, when the U.S. Centre for Disease Control and Prevention (CDC) reported the unexplained occurrence of Pneumocystis jiroveci (formerly P. carinii) pneumonia in five previously healthy homosexual men in Los Angeles and of Kaposi's sarcoma (KS) with or without P. jiroveci pneumonia in 26 previously healthy homosexual men in New York and Los Angeles[1].

The HIV/AID Shasposed many unprecedented challenges. Further, owing to the insidious and covert nature of the disease, the problem is compounded by a prevailing attitude of denial or resistance of complacency at all levels. The visible manifestation of HIV occurs only at the last stage.

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As a result, there is a visible lack of realization of the problem in the society. The reactive response, therefore, does not match the real magnitude and gravity of the problem[2].

HIV and AIDS cause a wide spectrum of diseases and manifestation. Approximately 60 % of patients of AIDS have neurological symptoms and 80 to 90 % are found to have neuropathological abnormalities at autopsy[3].

Neurological complication of HIV infection cause considerable morbidity and are often associated with high mortality[4]. The pattern in India appears to differ from the classical literature in that neurotuberculosis leads the list of opportunistic infections[3].

Indian Scenario

HIV/AIDS in India came into public view in 1986 with detection of first few cases of HIV in Chennai and first AIDS case in Mumbai in 1987. Presence of HIV-2 infection in India was reported for the first time from Mumbai in 1991[5]. Though India is a country with low HIV prevalence, it has the third largest number of people living with HIV/AIDS. Based on HIV sentinel surveillance 2008-09, it is estimated that India has an adult prevalence of 0.31% with 23.9 lakh people infected with HIV, of which, 39 % (9.3 lakh) are female and 3.5 %are children, while 83 % are the in age group 15-49 years. It is estimated that India had approximately 1.2 lakh new HIV infections in 2009[6].

MATERIAL AND METHODS

SOURCE OF DATA

Patents admitted in VIMS Hospital in medicine wards between December 2010 to June 2012, diagnosed or suspected to have HIV infection due to high-risk behaviour or due to clinical clues were screened for HIV-1 and HIV-2 by ICTC (Patient was said to be HIV positive when tested positive by 3 HIV test systems: Trispot test, Trilene test, Dot immunoassay).

Clearance has been obtained from the Vijayanagar Institute of Medical Sciences, Bellary ethical committee.

INCLUSION CRITERIA

1. Patients above 20 years presenting with neurological manifestations and diagnosed to be HIV seropositive by ICTC (Patient was said to be HIV positive when tested positive by 3 HIV test systems

EXCLUSION CRITERIA

1. Patients with pre-existing neurological disease and children.
2. Patients less than 20 years

METHOD OF COLLECTION

Data was collected in a pretested proforma by meeting the objective of the study. A detailed history, physical findings with thorough neurological examination and necessary investigation were recorded. Treatment and outcome were not included in this study.

Investigations

1. CD4 count
2. Trispot test, Trilene test, Dot immunoassay.
3. CSF analysis (where not contraindicated) – Protein, Glucose, cell count and type, AFB, Gram stain, ADA, India Ink preparation, VDRL and serology to detect specific infection.
4. Neuroimaging (CT/MRI) where required.
5. Chest Roentgenogram (X-ray) and sputum examination.
6. Serology to detect antibody to Toxoplasma, CMV and other opportunistic infection.

Observations and Results

547 seropositive HIV patients were admitted in VIMS Hospital in medicine wards between December 2010 to June 2012

58 patients with neurological manifestations were enrolled in this study (10.6%).

Symptoms and signs are shown in Table 1. CD4 count is shown in Table 2. CSF Analysis:

CSF analysis was helpful in differentiating types of meningitis. It was done in 54 patients. It was not done in 4 patients as it was contraindicated. Cell counts ranged from 02 to 1352 with mean of 191/microliter. Most cases had predominant lymphocytes. Cells >50 per cumm were seen in 41 cases (76 %); 35-CNS TB, 6-Cryptococcal Meningitis. Protein level ranged

from 26mg/dl to 450mg/dl with mean of 127 mg/dl. CSF abnormalities are seen in 67 % of the patients[7].

Imaging

Total 49 cranial CTs and 2 MRI was done. 30 Cranial CT's were normal. The most common abnormality was cerebral oedema 8, inflammatory exudates 3,5 had hypo dense lesion suggestive of infract, single lesion-1, multiple lesions-1. Hydrocephalous 1, All mass / enhancing lesions were diagnosed to be tubercular granuloma based on clinical, CSF analysis and treatment response.

2 MRI taken from suspected myelitis cases showed changes suggestive demyelination in thoracic spinal cord. CT scan abnormalities are seen in 70 % of the patients76. Levy et al10 have reported[7].

Patients (5.46%) of AIDS with cerebrovascular complication - 4 with infarcts (due to endocarditis). Mc. Arthur et al11 reported 9 cases (7%) of Cerebrovascular accidents (infarcts and Haemorrhage). Snider et al12 reported 6 (12%) cases and postulated granulomatous angitis as probable eitiopathology. Wadia et al13 in their study in Pune observed mass lesions in 16 % of the patients, single lesion in 24 and multiple lesions in 38. In the study by Puccioni et al14, 16 % had ring-enhancing lesions, 18 % had non-enhancing lesions and 8 % had normal cranial CTs.

Neurological Manifestations

Table 3 comparison of neurological manifestations CNS TB:

HIV increases TB infection by 2 folds while AIDS increases by 5 folds**.** The commonest neurological complication of HIV infection in this study was due to tubercular involvement of the nervous system. It was seen in 37 patients (63.7%). Of them, 35 had tubercular meningitis, 2 had intracranial tuberculomas. The diagnosis was made based on clinical, imaging CSF analysis and response to treatment. The mean age at diagnosis was 33.4yrs. Tuberculosis was the presenting manifestation in 22 cases, 26 were males. 8 cases had associated pulmonary involvement. 7 patients had past history of tuberculosis, 2 had radiological abnormality suggestive of healed PTB (no history) and 6 had active PTB. CT scan was done in 29, showed cerebral oedema in 6, inflammatory exudates in 3, Multiple lesions in 1, single enhancing lesions in 1, hydrocephalous in 1 and 17 were normal Table 4 CNS TB comparison

Commonest presenting features were fever, headache, altered sensorium, convulsions and less common was focal deficit. CSF analysis showed protein ranging from 45 to 450 mg/dl with mean being 133mg/dl, cells ranging from 86 to 680 cells/cumm and mean count of 188 with lymphocyte predominance. CSF pleocytosis indicate early CNS involvement in HIV infection. Berenguer et al16 compared clinical features and course of culture proven TBM with and without HIV infection and concluded the HIV infection did not alter the course of the tubercular illness and also response to treatment. Bisburg et al17 reported 10 cases of CNS TB in patients with AIDS and their findings Were similar to that of Berenguer et al. They advocate that TB should always be considered in the DD of CNS lesion in HIV infected individuals. Tuberculosis is wide-spread and rampant in our country, with a large segment of the population being constantly exposed to infection from open infected cases, irregular, incomplete therapy often results in partially treated and resistant cases. The poor hygiene and poor socio-economic states only compounds the problem. This accounts for the very high incidence of tubercular infection in HIV patients in our country. This is in contrast with the developed world where TB was almost eradicated and only the advent of HIV infection has seen the re-emergence of TB in the population.

Cryptococcal Meningitis

Meningitis manifested in 75 % of the cases. Tubercular meningitis was etiological agent in 35 cases (74.46%), Cryptococcus was the etiological agent in 9 cases (19.14%) and bacterial meningitis was seen in 3 cases (6.3%). Wadia et al63 reported meningitis in 17.88% of the 457 patients, Cryptococcal meningitis in 67.44% and tubercular in 18.60%. Table 5 Cryptococcal Meningitis comparisons.

In this study 9 patients were diagnosed to have Cryptococcal meningitis based on CSF India ink preparation. Mean age 34yrs, 6 males and 3 females. 7 had fever, 8 had headache and altered sensorium was seen in 1 patient, 2 had convulsions and history of weight loss was present in 5 cases. Candidiasis was seen with 4 patients. Signs of

meningeal irritation were present in6 cases. CSF analysis showed mean cell count of 67 per cumm, mean protein 100mg/dl and mean sugar of 40mg/dl. Cryptococcal antigen detection and culture was not carried out due to cost constraints and CSF India ink was the diagnostic criteria for all cases. Chunk et al18 found CSF India ink preparation for Cryptococci positive in only 50-70% of cases while Fernandes et al showed Indian ink positivity in 55% of cases. Hence a number of patients with Cryptococcal meningitis may have been missed in this study. Mean CD4 count was111, ranging from 34 to 262, 6 cases had count <100. Cranial CT was done in 8 cases. 7 were normal and 1 cerebral oedema. Levy et al10 reported 16 patients with Cryptococcal meningitis in their study, one of who developed an intracerebral cryptococcoma. They reported the few of their patients had no neurological sign and symptoms except for headache and subtle altered sensorium. Neuroimaging as well as routing CSF examination may be normal on many occasions. Chuck et al51 in their study of 89 patients found that only 21% of the patients had >20 white cells, per ml of CSF. Detection of Cryptococcal antigen had a high degree of sensitivity and was positive in nearly 90% of cases. Popovich et al19 in their study of 35 patients with intracranial cryptococcal infection, reported diffuse atrophy in 34% of cases, mass lesion (cryptococcoma) in 11%, hydrocephalous in 9% and diffuse cerebral oedema in 3% of cases.

Table 1. Symptoms & signs comparison

Symptoms	Present study (%)	Sircar et al [21](%)
Headache	53.4	65
Altered sensorium	60.3	36
FND	29.3	33
Convulsion	29.3	28

Table 2. CD4 count comparison

	CNS Tuberculosis	Cryptococcus
This Study	189	111
CDC Guideline	< 250	< 100
Jorge et al8	139	40
Crowe et al9	250-500	75-125

Table 3. comparison of neurological manifestations

	This study n=58	Levy et al10 n=315	Snider et al12n=50	McArthur11 n=186
A. Infections				
Tubercular meningitis	60.3 %	<1 %	-	1 %
Cryptococcal meningitis	15.1%	13%	4%	6%
Meningo encephalitis	-	34 %	36 %	23 %
Cerebellitis	-	-	-	-
Myelitis	3.4 %	1 %	-	4 %
PML	-	2 %	4 %	
Bacterial menigitis	5.1%	-	-	----
Gullian barre syndrome	1.7%	--	_-	----
B. Intracranial mass Lesion	3.4 % tuberculoma	10 % Lymphoma	14 % lymphoma	17 %
C. HIV encephalopathy	-	-	-	7.3 %
D. Primary Vascular complication	8.6 % infarct	1.5 % infarct	6 % hemorrhage	<1 %
E. Other				
Cranial neuropathies	1.7%	3 %	-	-
Toxopl.	-	32 %	10 %	8 %
P. Neuropathy	-	6 %	16 %	5 %
Myopathy	-	<1 %	-	-

Table 4. CNS TB comparison

	Present study n=37	Madid et al n=40	Jorge et al 8 =33	Berenguer et al16n=37
Fever	33 (89.1%)	69%	76%	89%
Headache	19 (51.3%)	62%	100%	59%
Alt. Sensoriun	28 (75.6%)	28%	29%	43%
FND	8 (21.6%)	30%	6%	19%
Convulsions	12(32.4%)	42%	10%	3%
Weight loss	11 (31.4%)			
Lymphadenopathy	8(21.6%)			14%
PTB	2-o 6-n			
Mean protein	133.1	T in 80%	T in 64%	52
Mean sugar/glucose	49.7			
Mean cell count	188.8	tin 78%	t in 53%	234
Miningeal enhancement (exudates)	3		19%	23%
Tuberculoma	2		6%	15%
Infarcts (vasculitis)	-		-	27%
Hydrocephalus	1		19%	42%
Mean CD4	170		139	78%

Table 5. Cryptococcal Meningitis comparisons

	This Study	Jorge et Al[8]	Chuck et al[18]	Millogo et al[22]	Jimenez et al[23]
Mean age	34			34	37
Symptoms					
Fever	7 (77.7%)	42%	90%	33%	69%
Headache	8 (88.8%)	57%	87%	75%	77%
Alt. Sensorium	1(11.1%)	42%	50%	39%	77%
Convulsions	2 (22.2%)	-	-	25%	-
FND	1 (11.1%)	14%	50%	-	31%
Weight loss	5(55.5%)	-		-	-

Cranial Neuropathies

7 patients in this study had cranial nerve palsy. It involved 7th nerve in all cases. causes was CNS TB (3), 3 due to CVA, one Bell`s palsy. Mc. Arthur et al65in their study found four patients with cranial neuropathies, these of them having facial nerve palsy due to aseptic meningitis and one due to lymphomatous meningitis. Levy et al10 in their study of neurological involvement of HIV infected 315 patients detected 8cases of cranial neuropathies and 25 cases of peripheral neuropathies, 5 patients had Bell's palsy. Wadia et al13 reported Herpes Zoster in 28.27% of the 457 patients studied.

Myelopathy / Myelitis

Spinal cord involvement in form of Myelitis was seen in two patients, both presenting with flaccid paraperesis with definite sensory level and sphincter disturbance of acute onset. In both cases MRI of the spine showed abnormal signal intensities in thoracic cord, suggestive of demyelination. Levy et al10 have reported a case of necrotizing ascending myelitis, which resulted incomplete quadriplegia. Culture of CSF in this patient yielded CMV. Milligo et al20 reported Myelitis 8% in his study in '99 in France.

CEREBROVASCULAR ACCIDENT / STROKE

In this study 5 cases presented with stroke, 3 cases had right sided hemiparesis and their 2 had left sided hemiparesis. Facial nerve was involved in 3 cases. His cranial all 5 cases were infract,

no haemorrhage was noted. Mc. Arthur et al11 reported 9(7%) cases of Cerebrovascular accident. Levy et al10 have reported 7(5.46%) cases of AIDS with Cerebrovascular complications – 4 cases with infarct.

Conclusion

- The following are the conclusion drawn from this study:
- The percentage of HIV patients with neurological manifestation is 10.6 % over 19 month study period and is on the rise.
- Neurological manifestations heralded HIV in 62 % of patients.
- Young adults are mainly affected.
- Sexual activity with CSWs is the major mode of transmission.
- Meningitis was the commonest manifestation 81%. 47 out of 58 patients comprising of 35 cases of Tubercular Meningitis, 9 cases of Cryptococcal Meningitis and 3 cases of bacterial meningitis.
- Tuberculosis is the commonest disease affecting nervous system (39/58) with 2 of these patients having intracranial space occupying lesion (tuberculoma) and rest meningitis.
- Neuroimaging studies and CSF analysis are useful in diagnosing in opportunistic infections of the nervous system.
- High index of suspicion is necessary to detect HIV in patients presenting with neurological symptom and to diagnose and treat the underlying cause.
- This is a small study carried out over stipulated period of time in a small population and does not indicate the true incidence or prevalence of the disease in the community.

It is important that we continue to develop new diagnostic tools, new therapies and new strategies for managing these complications of immune dysfunction.

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