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A study of clinical profile of HIV positive patients with neurological manifestations

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ABSTRACT

Introduction: Central nervous system (CNS) is among the most frequent and serious target of HIV infection in patients with profound immunosuppression. CNS problems occur mainly due to either primary pathologic process of HIV or secondary to opportunistic infection and neoplasm.
Aims and objectives: To study the clinical and investigation profile in diagnosis of HIV patients with CNS manifestation. To correlate CD_4 levels with CNS opportunistic infections.
Materials and methods: A prospective observational non-randomized clinical study of 50 HIV infected patients, showing clinical evidence of CNS involvement, admitted in tertiary care centre was done. Detail clinical history and CNS examination was carried out. CD_4 count was measured using standard flowcytometry. Investigations like MRI brain/electromyography-nerve conduction studies/cerebrospinal fluid (CSF) examination were done as and when required for diagnosis.
Results: HIV induced primary CNS illness was present in 30% while 70% cases were due to secondary CNS manifestation mainly due to opportunistic infection. Most common primary illness was distal symmetric polyneuropathy (DSPN) (22%), followed by Aids dementia complex (ADC) (4%) and acute inflammatory demyelinating polyneuropathy (AIDP)(4%). tuberculous meningitis (TBM) was the most common presentation as secondary CNS illness (34%), followed by cryptococcal meningitis (14%), toxoplasmosis (10%), progressive multifocal leucoencephalopathy (PML) (8%) and neurosyphilis (4%). Meningitis was presenting CNS manifestation in majority of patients. The commonest presentation of TBM was fever (64%), while headache for cryptococcal meningitis (71%) and seizures was that of toxoplasmosis (80%). Mean CD_4 count was 170 ± 80.1 in patients of DSPN, 131 ± 85.75 for TBM, 47.5 ± 36.8 for cryptococcal, 160 ± 77.4 for toxoplasmosis and 93 ± 65 for ADC.
Conclusion: High degree of clinical suspicion of nervous involvement in HIV patients at all stages help in early diagnosis and institution of specific therapeutic measures which in turn decrease mortality and morbidity.

1. Introduction

With an estimated 2.5 million people living with HIV (PLHIV), India has the third highest HIV burden in the world, after South Africa and Nigeria [1]. The total number of people living with HIV/AIDS in India was estimated at 2.4 million (19.3 –30.4) in 2009. Children (less than 15 years) account for 3.5% of all infections, while 83% are the in age group 15–49 years. The estimated adult HIV prevalence in India was 0.31% (0.25–0.39%) in 2009. The adult prevalence was 0.25% among women and 0.36% among men in 2009 [2]. It is estimated that India had approximately 0.12 million new HIV infections in 2009 [2].

The nervous system is among the most frequent and serious target of HIV infection, occurring in patients with profound immunosuppression. CSF findings are abnormal in about 90% of patients, even during asymptomatic phase of HIV infection [3]. Neurological disease is the first manifestation of symptomatic HIV

Abbreviations: ADC, Aids dementia complex; ATT, anti-tuberculous therapy; AKD, Alka K. Deshpande; ART, anti-retroviral therapy; AIDS, acquired immunodeficiency syndrome; AIDP, acute inflammatory demyelinating neuropathy; CCM, cryptococcal meningitis; CSF, cerebrospinal fluid; CNS, central nervous system; DSPN, distal symmetrical polyneuropathy; DOTS, directly observed therapy-short course; EMG-NCS, electromyography-nerve conduction studies; IL, Interleukin; HIV, human immunodeficiency virus; HNCI, HIV associated neurocognitive impairment; NCCT, non-contrast computerized tomography; NACO, National AIDS Control Organization; NIMS, Nizam Institute Medical Sciences; MRI, magnetic resonance imaging; MMSE, mini mental status examination; OSA, Ogun Shamsideen Abayomi; PML, progressive multifocal leucoencephalopathy; PPC, Paulo Pereira Christo; TBM, tuberculous meningitis; TNF, tumour necrosis factor; VDRL, Venereal Disease Research Laboratory.

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Table 1
Primary and secondary neurological illness observed in HIV positive patients.

Neurological illness	Types	Number (%) ($n = 50$)
Primary	Distal symmetric polyneuropathy	11 (22)
	Aids dementia complex	2 (4)
	Acute inflammatory demyelinating polyneuropathy	2 (4)
Secondary	Tuberculous bacterial meningitis	17 (34)
	Cryptococcal meningitis	7 (14)
	Toxoplasmosis	5 (10)
	Progressive multifocal leucoencephalopathy	4 (8)
	Neurosyphilis	2 (4)

Table 2
Clinical presentation in secondary neurological illness in HIV positive patients.

Clinical presentation	Neurological illness ($n = 29$)		
	Tuberculous bacterial meningitis	Cryptococcal meningitis	Toxoplasmosis
Fever	88%	57%	40%
Altered consciousness	64%	71%	33%
Headache	82%	71%	42%
Convulsion	35%	43%	60%
Focal neurological deficit	18%	–	49%
Signs of meningeal irritation	76%	57%	0%

infection in 10–20% of patients [4]. Approximately 40–70% persons with HIV have clinically evident neurologic disorders. Neurological problems that occur in HIV infected individual may be either primary to pathological process of HIV infection or secondary to opportunistic infections or neoplasms. It may be inflammatory, demyelinating or degenerative in nature. India appears to be fertile soil for HIV infection due to poverty, illiteracy and lack of sex education.

Although extensive studies on HIV and AIDS have been done in west, there is pressing need for elaborate studies in India owing to differences in social, economic, cultural and educational background.

This study has been conducted at one of the largest tertiary care centre and referral hospital in India. The institute is associated with an ART (anti-retroviral therapy)-centre which is one of the 120 ART centres established by National Aids Control Organization (NACO) in India. NACO is the central governing body for the control and management of HIV/AIDS in India. By the end of December 2010, a total of 14,311 PLHIV have been registered at this ART centre.

2. Aims and objectives

This study was carried out with the following aims and objectives:

- To study the clinical and investigation profile in diagnosis of HIV patients with CNS manifestation.
- To correlate CD_4 levels with opportunistic infections of the central nervous system.

3. Materials and methods

This was a prospective observational non-randomised clinical study conducted from 2008 to 2010 in 50 patients.

3.1. Inclusion criteria

Newly diagnosed cases of HIV infection presenting with manifestations of neurological disease in the age group of 18–49 years were included in this study.

Table 3
Mean CD4 count in neurological illness in HIV positive patients.

Neurological illness	Mean CD4 count ± standard deviation (SD)
Tuberculous bacterial meningitis	131.5 ± 85.75
Cryptococcal meningitis	47.5 ± 36.8
Toxoplasmosis	160 ± 77.4
Progressive multifocal leucoencephalopathy	157 ± 76.8
Neurosyphilis	105 ± 31.8
Aids dementia complex	93 ± 65
Distal symmetric polyneuropathy	170 ± 80.1
Acute inflammatory demyelinating polyneuropathy	281 ± 74.3

3.2. Exclusion criteria

Patients with history of neurological diseases like cerebrovascular accidents, epilepsy, parkinsonism etc., diabetes, alcohol and other drug abuses like narcotics, sedatives and hypnotics were excluded from the study (Tables 1–4).

None of the patients were on anti-retroviral therapy (ART) as these patients were newly diagnosed cases of HIV infection.

Detailed clinical history with special emphasis on consciousness, convulsions and headache was taken. Thorough clinical examination included mental status examination including MMSE, sensory, motor and cranial nerves examination.

Apart from routine investigations, CD_4 count was measured using standard flowcytometry. Diagnostic investigations like MRI brain with contrast, cerebrospinal fluid (CSF) examination and electromyography-nerve conduction study (EMG-NCS) were done as and when required. Final outcome was measured.

Table 4
Outcome of secondary neurological illness in HIV positive patients.

Neurological illness	Outcome (%) ($n = 29$)	
	Improved	Fatal outcome
Tuberculous bacterial meningitis	90.90	09.10
Cryptococcal meningitis	67.14	32.86
Toxoplasmosis	85.71	14.29

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4. Results

Most patients (78%) were 21–40 years of age. Male:female ratio was 2.9:1. Of these 90% had history of unsafe sexual exposure, 2% had history of exposure to blood and blood products while in 8% the probable mode of transmission was not known.

HIV induced primary illness was found in 30% while 70% cases were due to secondary CNS manifestations mainly due to opportunistic infections. Most common primary illness was DSPN (22%) followed by ADC (4%) and AIDP (4%). TBM was the most common presenting secondary CNS illness. It was found in 34% of cases followed by cryptococcal meningitis (14%), toxoplasmosis (10%), PML (8%). Neurosyphillis was found in 4% cases. Meningitis as presenting CNS manifestation constituted the majority of patients in our study.

The commonest presentation of TBM was fever (88%) followed by headache (82%) and altered consciousness (64%) while headache (71%) and altered consciousness (71%) were the most common manifestation of cryptococcal meningitis. CNS Toxoplasmosis had new onset seizure (60%) as the most common presentation. Mean CD4 count was 170 ± 80.1 in patients of DSPN, 281 ± 74.3 for AIDP, 131 ± 85.7 for TBM, 47.5 ± 36.8 for cryptococcal meningitis, 160 ± 77.4 for toxoplasmosis. For ADC, mean CD4 count was 93 ± 65. AIDP occurs at higher CD4 level due to autoimmune phenomenon. 70% of patients with CNS manifestation had CD4 less than 200. The most common finding on neuroimaging in HIV+ ve patients presenting with neurological manifestation was meningeal enhancement (46%). Patients of TBM had 9.1% mortality while toxoplasmosis group had 32.86% and cryptococcal meningitis had mortality of 14.29%. None of the patients were on anti-retroviral therapy (ART) as these patients were newly diagnosed cases of HIV infection.

5. Discussion

After the first detection of AIDS cases in summer of 1981 among homosexuals in USA, the number of HIV positive individuals and AIDS cases has increased explosively. The neurological problem that occurs in HIV infected individual may be either primary to pathological process of HIV infection or secondary to opportunistic infection or neoplasm. Damage to CNS may be direct result of viral infection of CNS macrophages of Glial cells or may be secondary to release of neurotoxins and toxin cytokines such as IL-1, TNF α, TNF β and IL-6 [3].

In our study, the incidence of neurological involvement was found to be maximum in age group of 21–40 years which correlates with study done by Sircar AR in which maximum incidence (77.9%) was found in age group of 21–40 years [5]. This is a social danger as this is the most productive group of society that is going to affect the growth of nation and the future generations also. Males have high chances of HIV infection and its neurological manifestations probably due to high risk sexual behaviour than females.

HIV associated neurocognitive impairment (HNCI), myelopathy, peripheral neuropathy, myopathy and aseptic meningitis are primary illnesses. In our study DSPN was the most common primary neurological illness followed by ADC & AIDP, which are comparable with result of Nizam Institute of Medical Sciences (NIMS) study [6]. DSPN can occur in any stage of HIV infection. It is mostly seen in patients with CD4 less than 200. DSPN can occur due to direct effect of virus or side effects of ART (mostly due to Stavudine or Didanosine) [3]. Although it is present clinically in 30–40% of patients, 2/3 of patients with AIDS may be shown by electrophysiological studies to have some evidence of peripheral nerve disease. AIDP is mediated by autoimmune mechanism. It is generally seen in patients with CD4 greater than 200. 4% of our patients had ADC which is diagnosed by MMSE score. It generally occurs when CD4 less than 100 [7].

In our study, 70% patients had neurological manifestations secondary to opportunistic infection or neoplasm, which was similar to the findings of other studies like NIMS, Ogun Shamsideen Abayomi (OSA) and the Brazilian study. Secondary neurological illness were found in 63% in the NIMS study and 65% in the Brazilian study [6,8,9]. TBM was the most common presentation as secondary CNS illness similar to the OSA and NIMS study, it was 26% in OSA and 25% in NIMS study [6,8]. Due to malnutrition, there are more chances of acquiring co-infection like tuberculosis in India. The commonest presentation of TBM was fever. It can be diagnosed by CSF examination and culture. CSF polymerase chain reaction (PCR) has high sensitivity to diagnose TBM [10]. Following TBM, cryptococcal meningitis, toxoplasmosis, PML and neurosyphillis were the other presenting secondary CNS illnesses which were similar to the NIMS and OSA studies [6,8]. In the Brazilian and Deshpande AK studies, toxoplasmosis was the most common cause of secondary CNS manifestation [9,11]. New onset seizure was the most common manifestation of toxoplasmosis followed by focal neurological deficit. MRI with contrast is the most sensitive technique to diagnose toxoplasmosis. It generally occurs in patients with CD4 less than 200 [3].

Cryptococcal meningitis generally occurs in patients with CD4 less than 100 and hence it causes minimal inflammation in patients with AIDS. Therefore there is frequent absence of neck stiffness and photophobia and CSF examination reveals absence of cellular response [3]. So high degree of clinical suspicion is needed. Headache was the most common manifestation of cryptococcal meningitis as also observed in Atilli suresh et al. study, followed by altered sensorium [12]. Fever, seizure and focal neurological deficit are less common symptoms. CSF cryptococcal antigen titre is the gold standard investigation for diagnosis [3]. PML results from infection with human polyoma virus–JC virus mostly at CD4 less than 100 and can be diagnosed by neuro-imaging [3].

In our study, the mean CD4 count was 170 ± 80.1 in patients with DSPN, 281 ± 74.3 for AIDP, 131 ± 85.75 for TBM, 47.5 ± 36.8 for cryptococcal meningitis, 160 ± 77.4 for toxoplasmosis. Our results are comparable with study conducted by Deshpande AK [11]. For ADC, the mean CD4 in our study was 93 which is comparable with the NIMS study in which mean CD4 was 92 [6].

Patients of toxoplasmosis and cryptococcal meningitis had higher mortality than TBM which matches with the study conducted by Attili VS et al. in which the mortality due to toxoplasmosis was 20% and 19% in cryptococcal meningitis [12]. Due to easy diagnostic methods and effective supplementation of anti-tuberculous therapy under directly observed therapy-short course (DOTS) strategy, mortality due to TBM was lower.

6. Conclusion

Neurological manifestations have been reported at all stages of HIV infection but detected especially in advanced HIV disease. So high index of suspicion of neurological involvement in HIV patients of all stages helps in early diagnosis and timely institution of specific therapeutic treatment which in turn considerably reduces the morbidity and mortality due to the disease.

Uncited reference

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