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Full Length Research Paper

Various neurological manifestations in HIV positive patients, their outcome and its correlation with CD_4 counts- A tertiary centre experience in North Indian population

M. L. Patel[1]*, Rekha Sachan[2], V. Atam[1], S. C. Chaudhary[1] and Abhinav Gupta[1]

[1]Department of Medicine, Chhatrapati Shahuji Maharaj Medical University, Lucknow, India.
[2]Department of Obstetrics and Gynaecology, Chhatrapati Shahuji Maharaj Medical University, UP Lucknow, India.

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The central nervous system (CNS) is among the most frequent and main target of HIV infection in severely immunocompromised patients. Neurological manifestations occur due to either primary pathologic process of HIV or secondary to opportunistic infection. The present study was conducted to ascertain the prevalence of various neurological manifestations in HIV positive patients, correlation of CD_4 levels in CNS opportunistic infection and their outcome. This was a prospective observational study of 105 HIV infected patients with clinical evidence of CNS involvement. A detailed clinical history and CNS examination was carried out. CD_4 counts was measured by flow cytometry method and other investigations like magnetic resonance imaging (MRI), brain/electromyography, nerve conduction studies and cerebrospinal fluid (CSF) examination were done as required for diagnosis. HIV induced primary illness was present in about 30% cases while 70% associated with secondary CNS manifestations were mainly due to opportunistic infection. The most common primary illness was distal symmetrical polyneuropathy (20.9%), followed by AIDS dementia complex (3.8%), acute inflammatory demyelinating neuropathy (3.8%). On the other hand, the most common secondary CNS infection was tuberculous bacterial (TBM; 32.3%), followed by cryptococcal meningitis (13.3%), progressive multifocal leukoencephalopathy (PML; 11.4%), and cerebral toxoplasmosis (9.5%). The commonest presenting symptoms of TBM were fever (72.38%), while headache and vomiting was 27.62 and 28.57%, respectively. Mean CD_4 count was 172 ± 81.2 in distal symmetrical polyneuropathy (DSPN), 282 ± 75.3 in acute inflammatory demyelinating neuropathy (AIDP) and 95 ± 6.5 for AIDS dementia complex.

Key words: HIV positive patients, CD_4 count, neurological manifestation.

INTRODUCTION

HIV infection is a global pandemic, with cases reported from virtually every country. What has become clear over the time is that HIV knows no boundaries, geographical, political or socioeconomic status. In 2009, approximately 2.4 million people were estimated to be living with HIV/AIDS in India (AIDS epidemic update, 2010). Children (<15 years) account for 3.5% for all infection, while 83% are in the age group 15 to 49 years. The estimated adult HIV prevalence in India was 0.3% in 2009, with adult male prevalence 0.36% and female 0.25% in 2009 (0.25 to 0.39%) (NACO, 2010) It is estimated that India had approximately 0.12 million new HIV infection in 2009 (NACO, 2010).

Neurological manifestations are seen throughout the

*Corresponding author. E-mail: patel.ml66@gmail.com. Tel: 9415154510.

Abbreviations: **ATT,** Anti-tuberculous therapy; **ART,** anti-retroviral therapy; **AIDS,** acquired immunodeficiency syndrome; **ADC,** AIDS dementia complex; **AIDP,** acute inflammatory demyelinating neuropathy; **CSF,** cerebrospinal fluid, **CNS,** central nervous system; **DOTS,** directly observed therapy short course; **DSPN,** distal symmetrical polyneuropathy; **EMG-NCS,** electromyography-nerve conduction studies; **IL,** interleukin; **HIV,** human immunodeficiency virus.

course of HIV disease from prodromal stage till terminal illness and all parts of neuroaxis can be involved. Symptomatic neurologic dysfunction develops in more than 50% of individual infected with HIV and neuropathological lesions are detected at autopsy in approximately 90% of cases. This may be explained by the fact that the central nervous system is a sanctuary site for HIV and there is poor penetration of antiviral drugs due to presence of intact brain barrier (Levy et al., 1985). The nervous system is among the most frequent and serious target of HIV infection occurring in patients with profound immune suppression. cerebrospinal fluid (CSF) finding are abnormal in about 90% of patients even during asymptomatic phase of HIV infection (Fauci and Lane, 2008).

Neurological problem is the first manifestation of symptomatic HIV infection in 10 - 20% of patients (HIV sentinel surveillance, 2007). Neurological manifestation may be either primary to pathological process of HIV infection or secondary to opportunistic infections or neoplasm. It may be inflammatory, demyelinating or degenerative in nature.

The neurological manifestations, natural course and outcome of HIV disease is likely to be different in India from other countries because of prevailing endemic infections, poverty, illiteracy, inability to take anti-retroviral therapy (ART) and malnutrition. The present study was carried out to assess the prevalence of various neurological manifestations in HIV positive patients, its correlation with CD_4 counts in central nervous system opportunistic infection and their outcome.

MATERIALS AND METHODS

This was a prospective observational study conducted at one of the largest tertiary care centre of Uttar Pradesh and the referral hospital for ART run under the aegis of the National AIDS Control Organization (NACO), the Chhatrapati Shahuji Maharaj Medical University, Lucknow Uttar Pradesh India. In total, 105 patients were studies from August 2009 to July 2010. Subjects fulfilling the inclusion criteria, with age more than 14 years and positive for HIV by standard NACO guidelines (2007) were enrolled in the study after written informed consent. Patients with history of neurological diseases like cerebrovascular accidents epilepsy, Parkinsonism, diabetes, alcohol and other drug abuses like narcotics, sedatives and hypnotics were excluded from the study. None of the patients were on 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 mental status examination, including mini-mental state examination (MMSE), sensory, motor and cranial nerve examination were done. Apart from routine investigations, CD_4 count was measured by standard flow cytometry method. Other diagnostic investigation like toxoplasma serology by double sandwich enzyme linked immunosorbent assay (DS-ELISA) kit, magnetic resonance imaging (MRI) of brain with contrast cerebrospinal fluid (CSF) examinations, and electrophysiological studies like electromyography-nerve conduction study (EMG-NCS) were done where required. However, viral load could not be done due to lack of facility.

RESULTS

A total number of 105 HIV infected patients were studied, out of which 80 patients were suffering from AIDS according to criteria of NACO and 25 patients were HIV positive but were not suffering from AIDS. Mean age of HIV positive patients with neurologic manifestation was 34.28 ± 7.8 years and majority of patients (49.5%) were 31 to 40 years of age; male: female ratio was 4.5:1, of these 75.2% are commercial sex workers and 5.7% had history of exposure to blood and blood product. One patient (0.95%) was a drug abuser and was therefore excluded from the study, while the rest of infected subjects' mode of transmission was not known. The commonest presenting symptom (Table 1) was fever (72.38%), followed by loss of weight (56.19%), vomiting (28.57), headache (27.62%), altered sensorium (18.1%), paraparesis (1.90%), blurring of vision (1.9%), hemiparesis (1.9%) and quadriparesis (0.95%).

CD_4 count could not be done in all patients, only 85 patients with neurologic manifestation were evaluated. Mean CD_4 count was 282 ± 75.3 in patients with acute inflammatory demyelinating polyneuropathy (AIDP), 172 ± 81.2 in distal symmetrical polyneuropathy (DSPN), 162 ± 78.5 for cerebral toxoplasmosis, 132.6 ± 86.78 for tuberculous bacterial meningitis (TBM), and 48.5 ± 37.6 for cryptococcal meningitis (Table 3). For AIDS dementia complex (ADC), the mean CD_4 count was 95 ± 6.5, AIDP occurred even at higher CD_4 level due to autoimmune phenomenon. Meanwhile, 49% of patients with central nervous system (CNS) manifestation had CD_4 count less than 200. The most common finding on neuro-imaging in HIV positive patients presenting with neurological manifestation was meningeal enhancement (67.5%), followed by hydrocephalous (11.4%). The highest mortality was present in cerebral toxoplasmosis group (33%), followed by cryptococcal meningitis (15.2%), while patients of TBM had (9.3%) mortality.

HIV-induced primary illness was found in 30%, while 70% cases were due to secondary CNS manifestations mainly due to opportunistic infection (Table 2). The most common primary illness was DSPN (20.9%), followed by ADC (3.8%) and AIDP (3.8%). TBM (32.3%) was the most common presenting secondary CNS illness, followed by cryptococcal meningitis (13.3%), cerebral toxoplasmosis (9.5%) and progressive multifocal leukoencephalopathy (PML) (11.4%).

DISCUSSION

After the first detection of AIDS cases on 5th June in 1981 among homosexuals men in USA, the number of HIV positive individuals and AIDS cases has increased at a logarithmic rate. HIV infection of central nervous system results in damage of brain tissue and there has been a geometrical increase in the incidence (Chandra et al., 2000). The neurological problem that occurs in HIV

Table 1. Common symptoms in HIV patients (N = 105).

Chief complaints	Number of patients	Percentage
Fever	76	72.38
Headache	29	27.62
Vomiting	30	28.57
Diarrhea	18	17.14
Generalized tonic-clonic severe	7	6.67
Altered sensorium	19	18.10
Paraparesis	2	18.10
Hemiparesis	2	1.90
Quadriparesis	1	0.95
Blurring of vision	2	1.90
Dysphagia	1	0.95
Anorexia	11	10.48
Slurring of speech	1	0.95
Loss of weight	59	56.19
Yellow discoloration	4	3.81
Ear discharge	1	0.95
Cough	23	21.90
Hemoptysis	2	1.90
Breath lessness	12	11.43
Generalized weakness	21	20.00

Table 2. Primary and secondary neurological illness observed in HIV patients.

Neurological illness	Types	Number (N = 105) (%)
Primary	Distal symmetrical poly neuropathy	22 (20.9)
	AIDS dementia complex	4 (3.8)
	acute inflammatory demyelinating polyneuropathy	4 (3.8)
Secondary	Tuberculous bacterial meningitis	34 (32.3)
	Cryptococcal meningitis	14 (13.3)
	Toxoplasmosis	10 (9.5)
	Progressive multifocal leukoencephalopathy	12 (11.4)

AIDP-Acute inflammatory demyelinating neuropathy.

infected individual may be either primary to pathological process of HIV infection or secondary to opportunistic infection or neoplasm. Damage to CNS may be a direct result of viral infection of CNS macrophages of glial cells or may be secondary to release of neurotoxins and cytokines such as IL-1, TNF- α, TNF-β and IL-6 (Levy et al., 1985).

In our study, the incidence of neurological involvement was found to be maximum in age group of 31 to 40 years (Mean 34.3 ± 7.8) which is compatible with study done by Sircar et al. (1998) in which maximum incidence was found in age group of 21 to 40 (Mean 34.9 ± 12) years. The age distribution was comparable to the study done by Teja et al. (2005) in which patients were in 30 - 40 age group. This is a social danger as this is the most productive age group of society that is going to affect the growth of nation and the future generations also. Males have high chances of HIV infection (4.5:1). Our study was also compatible to that done by Teja et al. (2005) (3:1) and Ghate et al. (2009) (6:1). Globally, women constitute half (50% [48 - 53%]) the adults (15 years and older) living with HIV in 2010, according to UNAIDS estimates. The burden of HIV on women, however, varies considerably by region and is heaviest in Sub-Saharan-Africa. In that region 1.4 times more adult women than men were living with HIV in 2010 (AIDS epidemic update, 2010).

HIV associated neurocognitive impairment (HNCI), myelopathy, peripheral neuropathy, myopathy and aseptic meningitis are primary illnesses. In our study, DSPN

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

Neurological illness	Mean CD_4 count ±SD (N=85)
Tuberculous bacterial meningitis	132.6 ± 86.78
Cryptococcal meningitis	48.5 ± 37.6
Toxoplasmosis	162 ± 78.5
Progressive multifocal leukoencephalopathy	158 ± 77.8
AIDS dementia complex	95 ± 6.5
Distal symmetrical polyneuropathy	172 ± 81.2
Acute inflammatory demyelinating neuropathy	282 ± 75.3

Table 4. Distribution of patients according to CD_4 counts.

CD_4 count	Total no. of patients	No. of patients with neurologic manifestation	Percentage of total no. of patients
<200	45	22	48.89
200-300	33	11	33.33
>350	7	2	28.57
Total	85	34	

Table 5. Outcome of secondary neurological illness in HIV positive patients.

Neurological illness	Outcome (N = 105)	
	Improved (%)	Fatal outcome (%)
Tuberculous bacterial meningitis	90.70	9.30
Toxoplasmosis	67	33
Cryptococcal meningitis	84.8	15.2

was the most common primary neurological illness followed by ADC and AIDP, which are comparable with result of NIMS study (Teja et al., 2005; Abayomi et al., 2005). DSPN can occur in any stage of HIV infection. It is mostly seen in patients with CD_4 less than 200. Moreover, DSPN can occur due to direct effect of virus or side effects of ART (mostly due to stavudine or didanosine) (Levy et al., 1985). Although it is present clinically in 30 to 40% of patients, 2/3 of patients with AIDS may be shown by electrophysiological studies to have some evidence of peripheral nerve disease. On the other hand, AIDP is mediated by autoimmune mechanism. It is generally seen in patients with CD_4 counts greater than 200. Four percent of our patients had ADC which is diagnosed by MMSE score (Table 4). Deshpande and Patnaik (2005) has reported ADC to be present in 5% of study population. It generally occurs when CD_4 less than 100 Teja et al., 2005).

In our study, 70% patients had neurological manifesttations 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 Nizam Institute Medical Sciences (NIMS) study and 65% in the Brazilian study (Sircar et al., 1998; Price and Brew, 1988; Okoror et al., 2008). 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 (Sircar et al., 1998; Price and Brew, 1988). The immune system of individuals is brought down due to emergence of the HIV infection. So these patients are very much prone to opportunistic infections like tuberculosis, Cryptococcus, fungal infection, etc (Okoror et al., 2008). 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 (Barnes et al., 1991). Following TBM, cryptococcal meningitis, toxoplasmosis, and PML were the other presenting secondary CNS illnesses (Table 5), which were similar to the NIMS and OSA studies (Sircar et al., 1998; Price and Brew, 1988). In the Brazilian (Oliveira et al., 2006) and Deshpande and Patnaik (2005) studies, toxoplasmosis was the most common cause of secondary CNS manifestation. 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 CD_4 less than 200 (Levy et al., 1985).

Furthermore, our study showed that the mean CD_4 count was 172 ± 81.2 in patients with DSPN, 282 ± 75.3 for AIDP, 132 ± 86.78 for TBM, 48.5 ± 37.6 for cryptococcal meningitis, and 162 ± 78.5 for toxoplasmosis. Our results are comparable with study conducted by Deshpande and Patnaik (2005). For ADC, the mean CD_4 in our study was 93, which is comparable with the NIMS study in which mean CD_4 was 92 (Sircar et al., 1998). Cryptococcal meningitis generally occurs in patients with CD_4 less than 100 and hence it causes minimal inflammation in patients with AIDS. Therefore, there is frequent absence of neck stiffness and photo-phobia and CSF examination reveals absence of cellular response (Levy et al., 1985). So, high degree of clinical suspicion is needed. Headache was the most common manifestation of cryptococcal meningitis as was also observed in the study of Attili et al. (2003), followed by altered sensorium. Fever, seizure and focal neu-rological deficit are less common symptoms. CSF cryptococcal antigen titer is the gold standard investi-gation for diagnosis (Levy et al., 1985). PML results from infection with human polyomavirus-JC virus mostly at CD_4 less than 100 and can be diagnosed by neuro-imaging (Levy et al., 1985).

In general, patients of toxoplasmosis and cryptococcal meningitis had higher mortality than TBM, which coin-cides with the study conducted by Attili et al. (2003) in which the mortality due to toxoplasmosis was 20 and 19% in cryptococcal meningitis. Meanwhile, due to easy diagnostic methods and effective supplementation of anti-tubercular therapy under directly observed therapy-short course (DOTS) strategy, mortality as a result of TBM was lower.

Conclusion

The most common secondary neurological illness was tubercular meningitis and the most fatal neurological illness was the toxoplasmosis. This study showed that in spite of good CD_4 count, there was an increase chance of neurological complications as seen with AIDP in which CD_4 count was 282 ± 75.3. Thus, we should be careful about the CNS involvement in HIV patient at all stages, so that this can help in early diagnosis, which in turns decreases morbidity and mortality.

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