Neurological complications in late-stage hospitalized patients with HIV disease

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Abstract

Background and Objective: The nervous system is the most frequent and serious targets of human immunodeficiency virus (HIV) infection. In spite of a wide prevalence of neurological manifestations in HIV there are not many studies to look into it, especially from this part of the world. We investigated various neurological manifestations of HIV and their association with CD4 and CD8 counts at the time of presentation. Materials and Methods: All HIV-infected patients who presented to 750 bedded teaching hospital in North India were subjected to thorough neurological and neuropsychological evaluation. Wherever indicated, neuroimaging, cerebrospinal fluid study, electromyography, and nerve-conduction studies were performed to confirm the diagnosis. CD4 and CD8 counts were calculated. Results: A total of 416 HIV-positive patients were seen. Of them 269 were males. A total of 312 neurological events were identified in 268 patients having evidence of neurological involvement. HIV-associated dementia (HAD) was the most common cause of morbidity (33.65%), followed by CNS infections (21.63%). Most common CNS infection was tuberculosis (65.56%). CD4 counts in CNS infections and HAD were 64.8/μl and 83.52/μl, respectively. Most of the patients in our study had low scores on MMSE (22.32). Conclusions: Even in the absence of overt neurological disease, subclinical involvement in the form of subtle cognitive and motor decline is found to occur with greater frequency. Most of these patients have lower CD4 and CD8 counts, thus substantiating the proposition that neuroAIDS is a late manifestation. Significant correlation exists between CD4 counts and type of neurological manifestation. We concluded that neuropsychological assessment should be mandatory for all HIV-positive patients.

Key Words

CD4 and CD8 cell counts, HIV-associated dementia, Folstein Mini Mental State Examination, neurological disorders, neuro AIDS

Introduction

The nervous system is among the most frequent and serious targets of human immunodeficiency virus (HIV) infection. 40% to 70% of all persons infected with HIV develop symptomatic neurological disorders.[3] Although nervous system involvement typically occurs with profound immunosuppression and in the presence of other acquired immunodeficiency syndrome (AIDS) defining illnesses, yet in 10% to 20% of HIV seropositive persons it heralds AIDS.

The nomenclature of HIV-related neurological diagnoses was recently revised and updated.[2,3] The neurological complications of AIDS (NeuroAIDS) include neoucognitive impairment and HIV-associated dementia (HAD; also known as AIDS dementia and HIV encephalopathy). HAD is the most significant and devastating central nervous system (CNS) complication associated with HIV infection. Less seriously afflicted patients manifest a milder form of HIV-associated impairment known as HIV-associated minor cognitive/motor disorder (MCMD).

In spite of the wide prevalence of neurological manifestations in HIV there have not been many studies to look into this aspect of the disease especially in the resource-limited communities in Sub-Saharan Africa, Asia, and the rest of the developing world.

Materials and Methods

The study was conducted over a 4 year prospective period and included all patients who satisfied the inclusion criteria (>18 year of age; HIV positive; any gender) from 1 January 2006 to 31 December 2009 and were admitted to the hospital medical unit or were referred to the outpatient department of Adesh Institute of Medical Sciences and Research, Bathinda.
All HIV-positive patients who presented to the hospital and susceptible family members of the HIV-positive patients were screened. If found seropositive, they were included in the study.

HIV infection was confirmed by a combination of ELISA and Western Blot. All patients were interviewed and examined. A detailed neurological examination and neuropsychological tests were done in all patients. Other diagnostic studies like peripheral nerve conduction studies (NCV), electromyography (EMG), neuroimaging and CSF studies were performed in selective patients.

All the patients included in the study had absolute CD4+ and CD8+ levels documented. For clinical staging of these patients we used the ’1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults’.[9]

Results

Age and sex distribution

A total of 416 consecutive HIV positive patients were observed. The age ranged from 20 to 65 years, in males, with the mean age being 40.98 ±11.42 years. In females the age was between 23 and 60 years with a mean age of 40.88 ± 11.57 years.

The peak incidence was seen in the fourth decade of life. Most of the subjects (269) were males with a male: Female ratio of 1.83:1.

Mode of acquisition of virus

85.09% patients acquired the infection through sexual route. Multiple unprotected heterosexual contacts with commercial sex workers was the major risk factor in 79.55% of male patients, while most of the females (84.35%) had acquired infection from HIV-positive husbands. 1.20% acquired infection through blood or blood products, while a large number (7.93%) were infected through the use of intravenous drugs. 3.85% of the patients had HIV-positive husbands. 1.20% acquired infection through blood transfusions. Most of the females (84.35%) had acquired infection from heterosexual partners and 36.84% of them acquired the infection through sexual contact, while most of the males (85.09%) acquired infection through homosexual contacts. The mode of transmission remained unidentified in another 5.77%.

Clinical categories according to CD4+ cell counts

The patients were categorized as shown [Table 1] Out of a total of 416 subjects, 309 (74.28%) had CD4+ counts of less than 200/μl, 251 (60.34%) fell into the category C (AIDS indicator conditions). 368 patients fulfilled the case definition for AIDS.

Neurological diseases in the patients

312 neurological events were observed during this study in the 268 patients having evidence of neurological involvement. HIV-associated dementia (HAD) was the most common cause of morbidity, being present in 33.65%, followed by CNS infections in 21.63%. The most common cause of CNS infections was tuberculosis, (65.56%) followed by cryptococcosis in 27.78%.

Table 2 shows the various neurological diseases observed in our study as compared with various studies.

0.72% patients had toxoplasmosis and an equal number had CMV involvement (including CMV retinitis). Tubercular meningitis was almost twice as common as compared to cryptococcal meningitis (59 v/s 25 cases).

Correlation of mean CD4 and CD8 counts and neurological disease

Most of the patients (88.23%) with CNS infections had relatively low level of CD4 counts, i.e. <200/μl. Most of the patients with HIV encephalopathy (HAD) had CD4 levels of <200/μl. Mean level of CD4 counts in patients having CNS infections were 64.8/μl compared to 152.93/μl in those without any neurological involvement. The levels of mean CD4 counts in HAD were 83.52/μl [Table 3]. The difference was statistically significant in tuberculosis, cytomegalovirus, and cryptococcus infections and HAD (P value <0.01). Similarly patients with tubercular, cryptococcal, and CMV infections had statistically significant difference in the levels of CD8 counts.

Correlation of mean CD4 and CD8 counts with peripheral neuropathy

Peripheral neuropathy was found in 42 patients. Patients with peripheral neuropathy had a mean CD4+ level of 110.6/μl. Patients without neuropathy had a mean CD4+ level of 138.6/μl. The patients with peripheral neuropathy had relatively higher level of CD4+ counts compared with patients having other neurological diseases. The most common type of peripheral neuropathy in these subjects was distal sensory polyneuropathy.

Correlation of MMSE score with CD4 and CD8 cell counts

We were able to do MMSE evaluation in 372 patients. Out of which 247 had low scores and 125 had normal scores. A definite cause accounted for the low MMSE levels in 107 patients. In the rest there was no such organic cause and thus a possibility of HAD was kept. The mean CD4 level was 90.68/μl compared to 152.93/μl in those without any neurological involvement. The difference was statistically significant in tuberculosis, cytomegalovirus, and cryptococcus infections and HAD (P value <0.01). The value was 150.63/μl in those without cognitive decline (MMSE levels ≤23). The mean CD4 level was 90.68/μl in those with cognitive decline. Hence, there was a statistically significant difference in the CD4 cell counts of patients with low score on MMSE as compared to those having a normal score.

Correlation of MMSE score with neurological disease

Most of the patients in our study had relatively low scores

Table 1: Clinical categories

| CD4+ T-cell categories | Asymptomatic, acute (primary) HIV or PGL | Symptomatic, not (A) or (C) conditions | AIDS indicator conditions | Total |
|------------------------|------------------------------------------|----------------------------------------|---------------------------|-------|
|                        | M F Total                                | M F Total                              | M F Total                 |       |
| >500/μl                | 2 0 2                                    | 1 2 3                                  | 1 1 2                      | 7     |
| 200-499/μl             | 4 10 14                                 | 23 12 35                               | 35 18 53                   | 102   |
| <200/μl                | 7 17 24                                 | 58 33 91                               | 138 54 192                 | 307   |

(According to 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS)
Table 2: Neurological manifestations (comparison of various studies in the published literature)

| Neuro-diagnosis                  | Our study/ Wadia et al (2001)% | Teja et al (2005)% | Satishchandra et al (2000)% | Deshpande et al (2005)% | Thorat et al (2004)% | Oliveira et al (2006)% | Stanley et al (2007)% | Kim et al (2003)% | Levy et al (2010)% |
|----------------------------------|---------------------------------|-------------------|-----------------------------|-------------------------|----------------------|-----------------------|-----------------------|----------------|-----------------|
| CNS infections                   | 21.63                           | 5.63              | 39.4                        | 80                      | 47                   | 39.22                  | 34.53                  | 46.0           | 2.94            |
| Tuberculosis                     | 14.18                           | 1.05              | 25.06                       | 34                      | 8                    | 18.5                   | 5.04                   | -              | 0.0             |
| Cryptococcus                     | 6.01                            | 3.79              | 10.95                       | 37                      | 17                   | 9.8                    | 5.99                   | -              | 2.94            |
| Toxoplasma*                      | 0.72                            | 2.69              | 9.25                        | 13                      | 20.33                | 5.8                    | 19.66                  | -              | 0.0             |
| CMV                              | 0.72                            | 1.11              | -                           | 1.33                    | 3.9                  | 0.72                   | -                     | 0.0            | 11.01           |
| SOL                              | 1.44                            | 5.04              | 27.5                        | 8                       | 21                   | 10.7                   | 0.24                   | -              | 5.88            |
| Peripheral neuropathy            | 10.10                           | 8.91              | -                           | 6                       | 8**                  | 4.9                    | -                     | 21.3           | 26.47           |
| Myopathy                         | 6.01                            | -                 | -                           | 0.33                    | -                    | -                     | 4.9                    | -              | 0.0             |
| Stroke                           | 1.44                            | 1.77              | -                           | 7.67                    | 16.6                 | 6.8                    | -                     | 6.8             | 0.63            |
| PML                              | 0.72                            | 0.98              | 1.7                         | 1.67                    | 3.9                  | 1.68                   | 2.94                   | -              | 0.63            |
| HIV associated dementia (HAD)    | 33.65                           | 1.38              | 8.03                        | 5                       | 1.33                 | 4.9                    | 2.16                   | 11.5           | 29.41           |
| No neurological manifestations   | 35.58                           | 70.07             | 74.41                       | 0                       | 0                    | 53.48                  | 50.8                   | 50             | 61.01           |
| Total                            | 416                             | 1527              | 1606                        | 100                     | 300                  | 102                    | 417                    | 61             | 34              |

*Toxoplasma has been included in focal mass lesions in some of the studies; **Includes cranial neuropathies too

On MMSE with an overall average of 22.32. The lowest levels of MMSE (18.75) were found in patients with CNS infections. Patients with HAD had slightly higher levels (mean of 20.33).

For obvious reasons, the patients with only peripheral neuropathy and myopathy had higher levels of 23.71 and 23.75 respectively. Thus we found statistically significant difference in the MMSE scores of patients with CNS meningitis (Tubercular, Cryptococcal and CMV) and HAD as compared to those having no neurological involvement.

Discussion

As our study was done on patients admitted to the hospital, most were symptomatic and as many as 368 out of 416 HIV-infected patients (88.46%) fulfilled the case definition of AIDS. The profile of opportunistic infection in our patients and in others reported from different centers from India revealed striking differences from those in North America and Africa. Contrary to the picture of AIDS in Africa, there was a conspicuous absence of Kaposi’s sarcoma, recurrent multidermatomal herpes zoster, and lymphoma. The difference in the spectrum of opportunistic infections in AIDS patients in India could possibly be due to the fact that AIDS patients in India die earlier due to endemic infections and do not survive enough to exhibit other opportunistic infections.

Neurological involvement has been documented in 5.75% of the 1061 HIV-positive patients in a study from South India.[8] Another study described neurological involvement in 4.4% of 1392 patients.[9] However, the worldwide prevalence of neurological complications in HIV appears to be much more than that.

A Pune-based study reported the results of neurological evaluation in 1527 HIV-reactive subjects.[7] Neurological complications were seen in 457 patients (481 neurological events). The prevalence was 20.24% of patients attending the outpatient clinic and in 44.57% in-patients. Earlier studies have reported that 40% of the patients suffering from AIDS had neurological manifestations.[8]

In our study a total of 312 neurological events were documented among 268 HIV-infected patients with neurological involvement. Quite a number of individuals had evidence of dual neurological involvement. The evidence of neurological involvement was found in 64.42% patients.

In 26 HIV-1 seropositive subjects with AIDS-related complex, 11 (42%) reported neurological, cognitive, or affective
symptoms compared with 30 (19%) of 157 HIV-1 seronegative subjects (relative risk 2.2, \( P = 0.02 \)). On neuropsychological testing, subjects with AIDS-related complex performed at a significantly lower level than the HIV-1 seronegative group.\(^8\) Prior to HAART, 40% developed neurologic disease and 30% of these had multiple lesions.\(^8\)

A study done on a cohort of 52 cases over a period of 4 years in India discussed the neurological involvements based on the clinical features, CSF analysis, CT (computed tomography) scan and the course of disease.\(^10\) It was found that 55% had meningoencephalitis, the most common being tubercular and fungal.

An earlier study has reported CNS infections in 17.88\%.\(^7\) Similarly in our study CNS infections were found in 21.63%. Since tuberculosis is the most common opportunistic infection in HIV disease in India, it would be expected to involve the CNS frequently and was the most frequent cause of meningitis in our study. The common spinal cord involvement was a compressive myelopathy secondary to Pott’s spine, although acute myelopathy (transverse myelitis) was also frequently observed. Three patients had evidence of tuberculoma [Figure 1] while two had brain abscess.

Most Indian studies document tubercular meningitis as being more common than cryptococcal meningitis.\(^7,11,12\) While diagnosis of tuberculosis is often presumptive, cryptococcal meningitis has been proven on CSF examination and toxoplasmosis has been diagnosed only after response to antitoxoplasma therapy along with a positive antibody screen in plasma.

Cryptococcal meningitis was the most common central nervous system fungal infection in HIV-infected patients in the United States. Around 5-10% of patients with AIDS develop cryptococcal meningitis.\(^13\) In our study, 25 out of 416, i.e. 6.01% of the patients with neuroAIDS had Cryptococcal meningitis. Fever, headache, and vomiting were the predominant complaints in them with some alteration of sensorium. However, neck rigidity was infrequent. The causative agent Cryptococcus neoformans may cause minimal inflammation in AIDS patients with impaired immune defense.\(^14\) This may explain why classic symptoms and signs of meningitis, such as neck stiffness and photophobia, are often absent. 89.6% of patients presented with neurological symptomatology, with headache and fever as the most common signs with variable meningeal signs.\(^15\) As seen in our study, cryptococcal meningitis occurred in later stages of HIV disease particularly with CD4 counts <100 \(\mu\)l.\(^12,16\)

A much lower proteins, normal sugar levels and lower number of cells were seen in the CSF of patients with cryptococcal meningitis than those with tubercular meningitis. Similar reports have been documented in other studies.\(^7\)

PML (progressive multifocal leukoencephalopathy) develops in 4% of patients with AIDS and was the initial manifestation of AIDS in 29% of these cases.\(^17\) The presenting symptoms of PML include altered mental status, speech, and visual disturbances, gait difficulty, hemiparesis, and limb incoordination. However, in our study only three patients had history, findings, and MRI picture suggestive of PML [Figure 2] The CD4 count in these patients were found to be on average 93/\(\mu\)l.

In our study neuropathy was diagnosed in 42 out of 416, i.e. 10.10% while the incidence of myopathy was 6.01%. It is similar to other studies which have reported the presence of neuropathies in 8-11% cases.\(^7,10\) Peripheral neuropathy is the most common neurological complication of HIV infection, affecting over one third of the patients according to a recent study.\(^18\) Distal sensory polyneuropathy (DSP) is the most common neurologic complication of human immunodeficiency virus (HIV) infection with 52% of the patients having symptomatic polyneuropathy.\(^19\) However, the incidence may be increased by the toxic effects of specific antiretroviral drugs on the peripheral nervous system.\(^20\) As most of our patients were drug naïve the chances of drug-induced neuropathy were less. Also the fact that most of our patients who developed neuropathy had higher cell counts is corroborated by a similar report of a higher CD4 count and older age as a risk factor for the development of DSP.\(^20\)

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**Figure 1:** Axial computed tomographic image showing multiple well-defined ring enhancing lesions with perilesional edema consistent with tuberculomas

**Figure 2:** Axial T2-weighted brain MRI. Diffuse white matter high signal intensities and cortical atrophy with ventricular enlargement consistent with a diagnosis of progressive multifocal leukoencephalopathy.
7.3% of patients with AIDS in the Centers of Disease Control (CDC) database were reported to have HAD.\[21]\] This figure is probably an underestimate because CDC figures generally reflect the incidence of disorder as the initial manifestation of AIDS, whereas dementia often occurs late in the course of HIV disease, following other AIDS defining events. The multicenter AIDS Cohort Study found a prevalence of HIV dementia of 0.4% during the asymptomatic phase, whereas retrospective studies have reported the prevalence of HIV dementia during late stages of HIV disease in the range of 7.5% to 27%.\[23,24]\] Most commonly dementia occurs late in HIV disease, after the patient has had other AIDS defining illnesses and when CD4 lymphocyte counts are below 200/mm\(^3\). HIV infection characteristically generates a “sub-cortical” pattern of neurocognitive dysfunction with deficits predominantly affecting executive functions, speed of information processing, attention/working memory, motor speed, new learning and retrieval of new information, while long-term (semantic) memory, many language skills, and visuospatial abilities may remain intact.\[25,26]\]

15-60% patients of AIDS develop AIDS dementia complex (HAD).\[27]\] Similarly in a study on children with HIV from India, 54.2% children had HIV encephalopathy.\[28]\]

The study of HIV in the context of psychiatric comorbidities and comorbid pathogenesis is in a fledgling stage despite epidemiological studies suggesting that >60% of HIV-infected individuals will suffer from at least one major psychiatric disorder during the course of infection.\[27,29]\] In our study HAD was found in 33.65% of the patients. Quite a large percent of patients in our study had a relatively low score on MMSE (mean of 22.32). However, although these had a low MMSE score, they were otherwise able to perform their daily activities in a normal way. Most of them did not provide any history of intellectual impairment or forgetfulness. Thus, subtle cognitive and intellectual decline was found in most patients who were HIV reactive even in the absence of clinical or overt neurological impairment. A relatively higher level of neurological impairment has been found in our study as documented in the MMSE score.

As ours is a tertiary referral centre, patients usually present to the hospital when they are severely immune compromised and hence have overwhelming opportunistic infections with relatively lower counts. These complications vary according to the stage of the illness. The presence of neurological complication as well as other clinical manifestations is associated with decreased CD4 and CD8 counts.\[30]\]

Conclusions

Although the main and direct target of HIV infection are the cells of the immune system, the nervous system is often damaged in the course of infection, not only by the disease processes that are secondary to immune dysfunction and its systemic manifestations but also by more fundamental effects of the retrovirus.

The neurological manifestations of HIV infection are both common and varied and they contribute significantly to patient morbidity and mortality. These complications include not only the more common opportunistic diseases but also the equally important HAD, with its characteristic motor and cognitive decline. Especially in resource-limited settings, where sophisticated neuroimaging technology is often unavailable, characterization of neurocognitive functioning through neuropsychological assessments including the Folstein MMSE is crucial to successful diagnosis and treatment. When assessments are reliable and valid, they are quite sensitive to even milder forms of CNS compromise and also may provide valuable estimates of functional impairment.

There is a significant correlation between the levels of CD4 counts and the type of neurological manifestations of HIV infection. The presence of neurological complications as well as other clinical manifestations is associated with decreased CD4 and CD8 counts thus substantiating the proposition that neurological involvement is usually a later manifestation when the level of immunodeficiency has achieved a higher degree. Thus neurological disorders with HIV infection might serve as an indicator for advanced HIV infection, immunosuppression and decreased CD4 cell counts. Neuropsychological assessment should be mandatory for all HIV-positive patients.

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