



A STUDY TO EVALUATE THE NEUROLOGICAL MANIFESTATIONS IN HIV PATIENTS

General Medicine

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ABSTRACT

The study involved 25 HIV positive patients who manifested with neurological complication. It included clinical, radiological and a monofilament study of the study group. Patients were selected from general ward, outpatient department of DR.D.Y.Patil Medical College and Hospital. Out of the 25 HIV patients included in the group, a detailed clinical examination was done and the following conclusions were reached. There was a clear male dominance of 15 patients (60%) in my study and most of the patients, (13 patients (52%)) were in their 3rd decade of life. The commonest symptom of presentation in the study group was burning pain, numbness in lower limbs and loss of weight (52%) followed by fever and headache (48%) and (40%) respectively. It was observed that the patients with a lower CD4 count were more symptomatic. The commonest manifestation seen in the study group was peripheral neuropathy in 52% of patients followed by meningitis in 40%. Other manifestations were PML and HIV dementia in 3 patients. Incidence of neurological complications were found more in patients who had their CD4 count <200 (64%). Peripheral neuropathy was the commonest manifestation, having HIV induced neuropathy as 40% and drug induced neuropathy as 12%. Neuropathies were more in patient with CD4 count <200 (32%). Commonest MRI findings in the study group were of PML in 16% followed by Tuberculoma in 9% patients and then Encephalomyelitis.

KEYWORDS

Cd4 COUNT, CNS MANIFESTATIONS, HIV, MINI MENTAL STATE EXAMINATION (MMSE), MONOFILAMENT STUDY, NEUROLOGICAL COMPLICATIONS, SPINAL SYNDROME, WHO REVISED CLINICAL STAGING OF HIV

AIMS AND OBJECTIVES

1. Clinical study of all HIV antibody positive patients who are presenting with Neurological manifestations.
2. Clinical, radiological and monofilament study of HIV positive patients Depending on the type of neurological symptoms manifested.

MATERIALS AND METHODS

A total of 25 patients has been studied who are HIV positive and having neurological manifestations. The cases were taken from general medicine wards and general outpatient department. Patients were asked a questionnaire and an informed consent was taken and detailed neurological examination was under taken. Detailed clinical history including history of exposure, history of blood transfusion history of drug abuse was taken. Onset, duration and progression of the disease was asked in detail. These patients were examined, including detailed general physical examination. Nervous system will be examined including higher mental functions, cranial nerve examinations, motor system and sensory system examination in detail

Duration of study: August 2010 to August 2012

INCLUSION CRITERIA

- Patients whose HIV antibodies are positive with neurological manifestations will be studied in detail.
- HIV patients who has induced neuropathy or myopathy.

EXCLUSION CRITERIA

- Paediatric age group under 12 years
- HIV positive patients who are not having any neurological involvement

NACO 2007 guidelines were sought for categorizing the patients according to the CD4 count and also for WHO guidelines for staging HIV patients on the basis of their manifestation. Relevant lab investigations were done on requirement basis as follows:

- 1 HMG
- 2 Platelets

CENTRAL NERVOUS SYSTEM MASS LESIONS

Patients, with AIDS presenting with change of mental status or an abnormal neurologic examination frequently have brain lesions on CT or MRI. These can be quite extensive and may represent life-threatening emergencies.

Toxoplasma Encephalitis

At the beginning of the AIDS epidemic, Toxoplasma encephalitis (TE) was the most common cerebral mass lesion in patients with AIDS. TE is caused by reactivation of latent infection by the protozoan Toxoplasma gondii as a result of progressive loss of cellular immunity. Since the era of HAART, there has been reduction in the incidence.

Clinical Presentation

Almost 90% of patients have CD4+T-lymphocyte counts less than 200/uL, and 75% have CD4+ counts less than 100/uL at the time of clinical presentation. The most common symptoms include headache, confusion, fever, and lethargy. Up to 30% develop seizures. 68% of patients have focal signs on the neurologic examination, such as hemiparesis, cranial nerve palsies, ataxia, and sensory deficits. The clinical presentation is usually subacute, ranging from a few days to a month.

Laboratory Investigation:

As is the case in the general population, serum anti-Toxoplasma IgG antibodies can be detected in patients with TE, whereas IgM antibodies are rarely found, supporting the notion that most cases represent a reactivation of latent infection, a negative serology points toward another entity, whereas a positive serology is not diagnostic.

Statistical analysis:

Analysis was done by SPSS (Statistical package for social science) software version II, using chi-square and t test. A p value < 0.05 is considered as significant. Study was started only after the permission of Institute of Ethical Committee and Confidentiality was strictly maintained in the study regarding the identity of the patients and the concerned data.

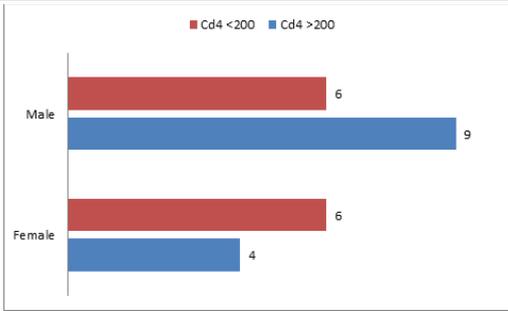
RESULTS

Out of 25 study participants 10 (44%) were females, 15 (60%) were males.

Distribution of study Participants According to the Gender				
	Frequency	Percent	Valid Percent	Cumulative Percent
Female	10	40.0	40.0	40.0
Male	15	60.0	60.0	100.0
Total	25	100.0	100.0	

Age group ranges from 18 – 60 years with mean age of 37.12.

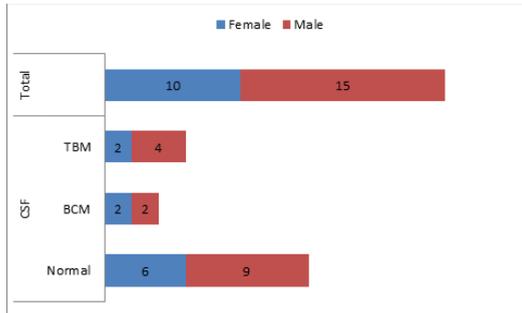
CD4 counts :



Among 10 females, 6 were having CD4< 200.Remaining 4 females were having more than 200.Among 15 males, 6 were having CD4<200 and 9 were having CD4> 200.

		Cd4		Total
		>200	<200	
Gender	Female	4	6	10
	Male	9	6	15
Total		13	12	25

CSF Analysis: Among 10 females 6 were having Normal CSF, 2 were having Bacterial meningitis, 2 were having Tuberculous Meningitis.

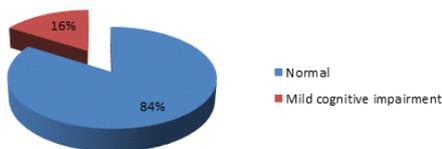


13(52%) were on SLN (Stavudine, Lamavudine, Nevirapine). Mini Mental State Examination(MMSE):

	Frequency	Percent	Valid Percent	Cumulative Percent
Normal	21	84.0	84.0	84.0
Mild cognitive impairment	4	16.0	16.0	100.0
Total	25	100.0	100.0	

Severe cognitive impairment = ZERO

MMSE

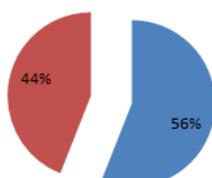


By using MMSE among 25 participants 21 (84%), were Normal.4 (16%) were Having Mild Cognitive Impairment.None of them were having severe Cognitive Impairment.

MRI:

MRI

■ Normal ■ Abnormal



Among 25 participants 14 (56%) were having Normal MRI Reports.Remaining 11(44%) were having abnormal reports.

Among 25, 7(28%) were having symptoms associated with vomiting.4 (16%) were having frequent seizure episodes.

Among 25 , loss of weight were reported in 13 (52%).Amon 25, 2 (8%) were having forgetfulness.Burning pain in lower limb were reported in 13 (52%) participants.Sensory loss was reported in 3(12%).

By using International HIV Dementia Scale (IHDS) / Sacktor Dementia Scale : among 25 participants 11 (44%) were in need of Further Evaluation for Dementia.

DISCUSSION

A 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 in Adesh Institute of Medical Sciences and Research, Bahinda. A total of 416 consecutive HIV positive patients with neurological manifestation were observed. The age ranged from 20to 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+ 11.57years.(1) The peak incidence was seen in the fourth decade of life. Most of the subjects (269) were males with a male; Female ratio of 1.83:1 138. In our study also male dominance was there but maximum incidence was in 3rd decade, but was statistically not significant.

SYMPTOM WISE DISTRIBUTION:

A symptom wise analysis and clinical evaluation was done at the time of presentation and during the period of hospital stay. Out of the 25HIV patients studied, the patients presented with various symptoms like fever, headache, vomiting, burning pain and numbness, loss of weight, neck stiffness, forgetfulness, sensory loss and seizures. The commonest presentations were loss of weight and burning pain and numbness in the lower limbs in 13 patients(52%).The next commonest being fever and headache in 12 patients(48%) and 10patients(40%) respectively. Next being neck stiffness elicited for 7 patients(28%) and seizure in 4 patients (16%) sensory loss in 3 patients (12%) and forgetfulness in 2 patients (8%) in the decreasing order(Table 2). In the study the incidence of a particular symptom in the patient was compared with the CD4 count of the respective patient, CD4 count range was divided as<200 and>200 (2). It was observed that the manifestation of symptom and signs were more common in patients who were having their CD4 count below 200 as compared to the patients who had a CD4 count more than 200 (Table 3).

PERIPHERAL NEUROPATHY WISE DISTRIBUTION

Out of the 25 HIV patients with neurological complications included in the study, 13 patients (52%) had manifestation of peripheral neuropathy (both primary and secondary incidence included).(Table 7). Most of the patients with peripheral neuropathy had the complaint of burning sensation in b/l lower limbs and numbness and almost all of them had either diminished or an absent ankle deep tendon reflexes. A monofilament test also was done in all the patients of the study group and was positive for all the 13 patients mentioned above. NCV studies were not done as it was not included in my methods. In the 13 patients with peripheral neuropathy in the group studied, 10 patient (76%) had neuropathy secondary to HIV-1 virus or infection(one case if CIDP included) and 3 patients (24%) had peripheral neuropathy induced by Stavudine therapy. The type of neuropathy is distal sensory polyneuropathy(DSP). This is the most common cause of peripheral neuropathy in HIV-1 infection, which is symptomatic in 35% of patients and asymptomatic in an additional 20%. This condition occurs generally in patients with advanced immunosuppression and may be more severe in those with an increased plasma HIV-1 viral load(3). The 13 patients with peripheral neuropathy in the study group was also compared with respectiveCD4 count each patients (Table 8). It was observed that patients with low CD4 count <200 was more prone for peripheral neuropathy which actually supports the data mentioned above. There were 8 patients with CD4 count <200 having peripheral neuropathy(61.5%) and 5 patients who had their CD4 count>200(38.4%).

This is a clinical study of patients who are HIV positive presenting with neurological manifestations. A detailed clinical, radiological, and monofilament test evaluation has been done in the study group.

The total number of patients studied were 25 all of whom were HIV positive and manifesting with neurological complications. Even drug

induced complications were included in the study group. The patients were drawn from general wards and out-patient department of DR.D.Y.Patil Medical College Pimpri. After detailed clinical examination and relevant investigations (radiological, laboratory and monofilament studies) various observations were found, which are being discussed here below in detail.

AGE AND SEX DISTRIBUTION:

In our study of HIV patients with neurological manifestations, there were 5 patients who were below 30 years of age, 13 patients who were in their third decade of life and 7 patients who were more than 40 years of age (Table 1). As the observation made from the above data, in our study it was seen that there was an increased incidence of neurological complications in patients who were in their 3rd decade of life (52%) as compared to <30 years (20%) and >40 years (28%).

Coming to the sex wise distribution and observation of the study group, it was seen that the number of male patients were 15 (60%) and number of female patients were 10 (40%) in total of 25 patients. And when compared sex to the age group, there were 3 males (60%) and 2 females (40%) who were <30 years of age, 8 males (61.5%) and 5 females (38.5%) who were in their 3rd decade, and 4 males (57.1%) 3 females (42.8%) who were >40 years.

So from the above observations in the study group of 25 HIV patients, it was seen that, the neurological complications were common in patients who are in their 3rd decade of life and there was a clear male sex dominance in all the age groups.

MUSCULOSKELETAL SYNDROMES

Muscular disorders have been described in HIV-1 –infected individuals and can occur at any stages of the disease.

Myopathy

Clinical Presentation:

Myopathy occurs in 17% of patients treated with zidovudine for periods over 270 days (4) and in 0.22% of HIV- infected patients who are not taking this medication (5). The clinical presentation is similar in these two groups. Patients complain principally of lower extremity weakness, characterized by difficulty in rising from a chair or climbing stairs as well as fatigue. Myalgias are present in up to half the cases, and the neurologic examination reveals proximal symmetric weakness, predominant at the level of the hip flexors (6).

Laboratory Investigation:

There is a mild elevation of creatine phosphokinase in the serum (median, 500 IU/L), although CPK can be as high as 7500 IU/L in some cases (7). This may be an incidental finding that orients toward a diagnosis in cases where muscle strength is still intact. The creatine phosphokinase level correlates with the degree of myonecrosis seen on muscle biopsy but not with the weakness.

Electrophysiologic Studies:

Electromyographic testing may reveal myopathic motor unit potentials with early recruitment and full interference patterns, predominantly in proximal muscles (6). But it can also be normal in 30% of the cases (7). Therefore, a normal electromyogram does not rule out this diagnosis.

Muscle Biopsy:

The etiology of myopathy in AIDS has been a matter of debate (8), because both HIV-1 and zidovudine presenting with myopathy, the most common finding is scattered. It was observed that the mean MMSE score was less in those patients who had a CD4 count less than 200. Hence showing that the cognitive impairment is more for patients who had a lower CD4 count <200 which is directly proportional. They had a mean score of 24.42 (12 patients 48%). This comparison of MMSE to CD4 count was found to be statistically significant. (P value < 0.05). Singh R et al conducted a prospective study 2006-2009 in which MMSE evaluation in 372 patients were done, 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/ul in those with cognitive decline (MMSE levels < 23). The value was 150.63/ul in those without 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 (1). As seen in the study mentioned above,

in our study also we had a statistically significant association of low MMSE score to decreased CD4 count (P value < 0.05). Hence it can be said that the cognitive impairment increases with decreased CD4 count.

CSF INFERENCE AND COMPARISON WITH CD4 COUNT

CSF studies were done in all the 25 HIV patients in the study group, 15 people had normal CSF picture (60%). In the rest of the 10 patients (40%), 6 people had Tubercular Meningitis (60%) and the rest of the patients had bacterial meningitis. Tubercular Meningitis patient had predominantly lymphocyte in their CSF and Bacterial meningitis predominantly had polymorphs. The CSF picture was compared to their respective CD4 count. It was observed that the incidence of meningitis (Both Tubercular and Bacterial) is more in patients who had a lower CD4 count of <200 as compared to higher CD4 count. Tubercular meningitis was the common one than Bacterial meningitis in both the group. The frequency of incidence of the symptom was similar as described earlier as loss of weight and burning and numbness in lower limb, fever, headache, neck stiffness, vomiting, sensory loss, seizures and forgetfulness in the decreasing order.

The symptoms of presentation of patients with advanced HIV being fever, weight loss, severe burning foot decreased cognitive function like forgetfulness and other manifestations indicating advanced disease or AIDS (2,3,9). In our study also the commonest symptoms were loss of weight, burning and numbness in lower limbs and fever, but was not statistically significant.

PRIMARY DIAGNOSIS WISE DISTRIBUTION:

In the 25 HIV patients with neurological manifestations studied in the group, the primary manifestations (associated secondary manifestations not included) were analysed clinically. (Table 4)

In the group, the most common manifestation what patients had was peripheral neuropathy for 8 patients (32%) (patients who had only peripheral neuropathy as primary diagnosis was included and 5 patients who had neuropathy as an associated symptom in not included in the Table). Tubercular meningitis being the second commonest manifestation in 6 patients (24%) (4 patients who had bacterial meningitis as an associated feature with other primary manifestations are not included in the table which will be subsequently discussed). Next commonest was tuberculoma and HIV-encephalopathy in 3 patients each (12%), followed by stroke and epilepsy in 1 patient (4%). 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 (14). 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 (1,10)

The different neurological manifestations in the study group of 25 patients were also compared with the CD4 count of respective patients. And it was found that the presentation of neurological manifestation were more seen in patients who had their CD4 less than 200, 16 patients (64%) compared to the patients who had CD4 counts more

SPINAL SYNDROME

Myelopathy is frequent finding at autopsy in patients with AIDS and is probably under recognized clinically. It can be primarily HIV-1 associated or caused by other opportunistic infections or tumors

Vacuolar Myelopathy

Vacuolar myelopathy (VM) is present in 17% to 46% of patients with AIDS at autopsy (11, 12, 13). This disorder occurs with advanced immunosuppression, and the symptoms are often overlooked or attributed to debilitation.

Clinical Presentation:

Symptoms are often overshadowed by coexisting central or peripheral nervous system impairment, such as AIDS dementia, which occurs late in the course of the disease (11). Usually, patients complain of progressive, painless gait disturbance, weakness and sensory disturbance, weakness and sensory disturbances in the legs, as well as importance in men, and urinary frequency.

Treatment:

Although the pathophysiology of AIDS dementia is not entirely elucidated, HIV-1 remains the main triggering factor, and it is therefore reasonable to prevent viral replication within the CNS. Antiretroviral drugs have variable penetration through the BBB, and evaluation of CNS concentration and pharmacokinetics of these medication is incomplete (14). zidovudine (AZT) has the highest CSF/ plasma ratio of all antiretroviral drugs, and at doses of 1000 to 2000 mg/day, this drug has been shown to induce clear improvement in patients with HIV-1-associated dementia, after 16 weeks of treatment compared with placebo (15) and declining incidence of AIDS dementia was documented after its introduction (16).

In any event, such high doses are not currently administered to patients because they cause myelosuppression with anemia and leucopenia. Other nucleoside analogue reverse transcriptase inhibitors (NRTIs) with documented penetration through the BBB include stavudine (d4T), which also causes peripheral neuropathy, and abacavir.

Among non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), nevirapine has a better penetration through the BBB than efavirenz, although both improved CNS function as determined by electrophysiologic motor tests in patients with psychomotor slowing. When added to two NRTIs (17) A trend toward better results with nevirapine compared with efavirenz did not reach statistical significance.

Clinical Presentation:

The most of symptoms is generally subacute, lasting weeks to months, Confusion, lethargy, and memory loss are the most frequent symptoms. As the disease progresses, hemiparesis, aphasia, seizures, and cranial nerve palsies occur (18) Fever, headaches, and constitutional symptoms are generally absent, which helps distinguish PCNSL from TE. At the time of diagnosis, the average CD4+T-lymphocyte counts are usually very low, around 50/UL.

Laboratory Investigation:

A mild mononuclear pleocytosis (<30 cells/UL). And elevation of the protein concentration in the CSF is a common finding in patients with PCNSL but is nonspecific and may be due to the underlying HIV-1 infection

High protein levels (up to 590 mg/dL) have been reported in patients with extensive lymphomatous infiltration of both cerebral hemispheres.

It is important to perform cytologic analysis of the CSF because the presence of atypical or malignant lymphomatous cells can establish the diagnosis. PCNSL do not metastasize systematically. Epstein-Barr virus (EBV) genome can be detected in tumor cells of nearly all primary central nervous system lymphoma tissue from patients without immunodeficiency (19). Detection of EBV DNA by PCR in the CSF has a sensitivity of 80% to 90% and a specificity of 87% to 98% for the diagnosis of PCNSL. Measurement of EBV CSF viral load by quantified PCR in the CSF may improve the sensitivity of this test and be clinically useful in monitoring responses to treatment (20).

Imaging Studies

The head of CT or MRI usually shows findings consistent with a CNS tumor. Solitary mass lesions are as frequent as multiple lesions (18). Most lesions display some degree of enhancement, which is usually nodular or patchy. Ring enhancement, identical to that commonly seen in TE, can occur and correlate with central tumor necrosis. Subependymal enhancement seems more specific of CNS lymphoma, but this is a rare feature. Lesions are frequently located in the corpus callosum, the periventricular white

Secondary Prophylaxis:

Standard maintenance therapy consists of pyrimethamine 25 to 75 mg/day with folic acid 10 mg daily and either sulfadiazine 2 to 4 g/day in four divided doses or clindamycin 300 mg orally 4 times a day or 450 mg orally 3 times a day. Patients with sustained CD4+T-cell counts above 200/UL for more than 3 months can discontinue their secondary prophylaxis (21).

If the diagnosis is made in a timely fashion and the patient does not become intolerant to the treatment. TE is currently an opportunistic

infection with a relatively high therapeutic success rate, and death is usually caused by other complications of AIDS.

Additional smaller enhancing lesions can be seen on coronal cuts in the right thalamus and at the left convexity (first) and in the right cerebellum and right temporal lobe (second). (source from principles and practice of Infectious Diseases, Mandell)

Primary Central Nervous System Lymphoma

This condition which affected 2% of patients with AIDS at the beginning of the epidemic, has seen its incidence decrease considerably in the HAART era. In 1998, it accounted for only 12% of AIDS-related focal brain lesions. Its radiographic appearance makes it the principal differential diagnosis of TE.

Electrophysiologic Studies:

Demyelination is demonstrated by reduced motor nerve conduction velocities or prolonged distal latencies and minimum F-wave latencies in two or more nerves. Conduction block is often prominent.

Nerve Biopsy:

Sural nerve biopsy generally demonstrates the presence of a perivascular and endoneurial mononuclear cell infiltrate with macrophage-mediated segmental demyelination.

Treatment:

Spontaneous recovery is usually the outcome of AIDP, although HIV-1-infected patients tend to have a more severe course with a slower recovery than immunocompetent individuals with GBS. Plasmapheresis is indicated if the illness is sufficiently severe to warrant treatment.

Patients with CIDP benefit from treatment with prednisone or plasmapheresis (22, 23) Prednisone should however be used with great caution in patients with immunosuppression. Other treatment such as intravenous immune globulin have also been used successfully in HIV-1-positive patients with inflammatory demyelinating polyneuropathy, sometimes in combination with plasmapheresis (24). Distal Sensory Polyneuropathy

Human Immunodeficiency Virus Associated:

This is the most common cause of peripheral neuropathy in HIV-1 infection, which is symptomatic in 35% of patients and symptomatic in an additional 20% (25). Moreover, histologic abnormalities can be detected at autopsy in most patients dying with AIDS (26). This condition occurs generally in patients with advanced immunosuppression and may be more severe in those with an elevated plasma HIV-1 viral load (27, 28) However, debilitating distal sensory polyneuropathy (DSP) can also occur in patients with undetectable plasma viral load and elevated CD4+T-cell counts.

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