Pak J Med Res
Vol. 57, No. 3, 2018

Original Article

Neurological Manifestations of HIV-AIDS among HIV diagnosed Patients at a Tertiary Care Hospital of Khyber Pakhtunkhwa, Pakistan

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Abstract

Background: Neurological manifestations affecting the nervous system at all stages of Human Immunodeficiency Virus (HIV) infection are common. Neurological complications occur in more than 40% of patients with HIV infection. They are the presenting feature of Acquired Immune Deficiency Syndrome (AIDS) in 10-20% of cases. At autopsy the prevalence of neuropathological abnormalities is 80%. Although an ongoing decline in HIV associated Central Nervous System (CNS) diseases has been observed in very recent years, the mortality from these diseases remains high.
Objective: To study the type and frequency of different neurological involvements in patients with HIV infection at tertiary care hospital in Peshawar, KPK and to correlate them with CD4 counts.
Study design, settings and duration: This retrospective observational study was carried at Lady Reading Hospital, Peshawar, KPK, Pakistan over a period of 8 years from May 2009 to June 2017.
Subjects and Methods: A total of 100 HIV sero-positive patients of both genders, aged >18 years, showing clinical evidence of central nervous system (CNS) involvement were included. Their clinical manifestations, laboratory investigations, and neuroimaging were studied. Laboratory investigations along with magnetic resonance imaging (MRI), EEG and nerve conduction study of the brain/spine was also performed.
Results: Tuberculous meningitis was the most common presentation as secondary CNS illness (49%), followed by cryptococcal meningitis (16%) and cerebrovascular accidents (7%). Furthermore, 6% had neurosyphilis, 5% had acquired immune deficiency syndrome (AIDS) associated dementia and peripheral neuropathy occurred in 17% of the patients. Headache was the most common neurological symptom seen in 42% of the patients. Seizures were noted in 35% of the patients. CD4 was significantly low in most of the patients with progressive multifocal leukoencephalopathy, HIV associated encephalopathy (HAD) and cryptococcal meningitis compared with other neurological manifestations. CD4 counts in tuberculous meningitis and HIV associated encephalopathy were 115/µl and 83/µl, respectively.
Conclusion: CNS tuberculosis was the most common secondary infection seen in HIV patients followed by cryptococcal meningitis. A high index of clinical suspicion of neurological involvement in HIV patients helps in the early diagnosis and early institution of specific treatment, which in turn decreases the morbidity and mortality considerably. Early treatment and prophylaxis of neurological problems in HIV patients is very important to decrease the mortality rate.
Key words: Tuberculous meningitis, cryptococcal meningitis, HIV, neurological manifestation, CD4.

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Received: 16 November 2017, **Accepted:** 28 September 2018, **Published:** 29 September 2018

Authors Contribution

YK conceptualized the project. SA & BA did the data collection. YK & AT performed the literature search. Statistical analysis was done by AK. YK, AT & AK also did the drafting, revision and writing of manuscript.

Introduction

The causative agent of acquired immunodeficiency syndrome (AIDS) is human immune deficiency virus (HIV). An estimated 37 million persons worldwide are infected with HIV. The main cause of its spread in both men and women is heterosexual mode.[1]

In Pakistan, the HIV epidemic is still in infant stage and according to UNAIDS fact sheet 2016 report there are about 130,000 to 150,000 people are affected. In Khyber Pakhtunkhwa (KP),

the high rate of HIV infection is because of male sex workers, unsafe blood transfusion, and irrational use of injection practices.[2] Additionally, other factors like illiteracy, overseas employment in gulf, poverty, lack of sex education, high prevalence of intravenous drug users and high prevalence of sexually transmitted diseases (STDs) particularly in transgender are the contributing factors in the transmission of HIV.[3]

In Pakistan, the HIV patients have higher chances of progressing to full-blown AIDS and developing neuro-tuberculosis, because patients either do not seek medical advice because of social stigma, do not take antiretroviral treatment (ART) or become ART defaulters. The AIDS epidemic in KPK Pakistan is still in its infancy.[4] However, HIV-positive individuals may become significant threat in the coming years, and will affect the planned national economy and health setup.

The nervous system is extensively involved in HIV and no part of nervous system being immune to the virus. Therefore, the knowledge about central nervous system (CNS) complications of HIV is very important for medical professionals. However, limited studies are available regarding the neurological manifestations of HIV/AIDS in Pakistan. Despite the high prevalence rate of HIV neurological manifestations, not a single study on this topic has been conducted in Khyber Pakhtunkhwa, Peshawar Pakistan.

Subjects and Methods

The study was retrospective cross sectional study conducted over a period of 8 years from May 2009 to June 2017 at a tertiary care Hospital, Government Lady Reading Hospital Peshawar Pakistan. Total 100 HIV patients with neurological manifestations were included. HIV patients with neurological manifestations having incomplete data were excluded from the study. It is the main tertiary care hospital of KP Province, which also caters for FATA and adjoining parts of Afghanistan. A detailed history was noted in each patient with special emphasis on history of sexual contacts, drug abuse, travel abroad, penile or vaginal ulcers, surgical interventions, blood transfusions or a history of tuberculosis, recurrent herpes zoster, seizures, unconsciousness or headache. Detailed physical examination was carried out in each patient to look for opportunistic infections. Fundus was examined in each patient. Routine biochemical, hematological, and bacteriological testing including liver and kidney function tests, complete blood count, cerebrospinal fluid (CSF) examination (cytology, sugar, proteins), special staining studies (Ziehl–Nelson stain, Indian ink, etc.), chest X-ray, and (cryptococcal and toxoplasmosis antigen with specific antigen detection tests in the serum and VDRL) were performed. CD4 count was done for all the study participants. All patients underwent reactive fluorescent treponemal antibody tests. Magnetic resonance imaging (MRI), EEG and nerve conduction study of the brain/spine were also performed.

Every patient's information was kept highly confidential. Patients with a diagnosis of neuro-AIDS were treated according to WHO guidelines[5,6] using first line antiretroviral treatment (ART), antituberculous, antifungal medications, antiviral, antibiotics, and anticonvulsants and anti-psychotic medications. Associated opportunistic infections were treated with respective drugs. Intensive care unit management and mechanical ventilation were provided whenever required. Patients having CD4 count <5000 cells/µL were put on Highly Active Antiretroviral Therapy (HAART) as recommended.[5,6] Chemoprophylaxis and ART categories was instituted as indicated. Trimethoprim–sufamethoxazole was given to prevent pneumonia in all patients with a CD4 lymphocyte count of <200cells/ml. Fluconazole and azithromycin was used for fungal and MAC complex prophylaxis. Data was entered and analyzed using SPSS version 16.

Results

A total of 100 patients were admitted with neurological manifestations of HIV/AIDS. The mean age of patient was 36±19 (range 18-55 years). Male to female ratio was 2:1. Thirty one percent (31%) patients had a primary neurological illness, whereas 69% patients had secondary illnesses (Table-1).

Table 1: Age and gender wise distribution of study population.

Particulars	*Patients (n= 100)*
Age	
18 – 30	22
31 – 40	45
41 – 50	25
Above 50	08
Gender	
Male	75
Female	25

Out of 100 patients with a neurological manifestation, 59 (59%) presented with fever. Headache was reported in 42 patients (42%), while 35 patients (35%) presented with a history of convulsions. Altered sensorium was the presenting complaint in 62 patients (62%). Vomiting was present in 35 (35%) patients. Twenty-seven (27%) patients presented with tingling and numbness. Forty-one

(41%) patients presented with focal deficits. Bladder and bowl involvement was found in 40 (40%) patients. Signs of meningeal irritation were present in 55 (55%) patients (Table-2).

Table 2: Clinical manifestations in the presence of neurological illness in HIV positive patients.

Clinical presentation	*No. of cases*	*%*
Fever	59	59
Altered consciousness	62	62
Headache	42	42
Convulsion	35	35
Tingling and numbnesss	27	27
Vomiting	35	35
Forgetfulness	12	12
Bowel and bladder impairment	40	40
Focal neurological deficit	41	41
Signs of meningeal irritation	55	55

Result showed that majority of the females (78%) acquired infection from their HIV positive husbands and 65% among total number of patients acquired infection sexually. The study provided that 08% patients acquired HIV infection through blood or blood related products and 18.5% patients were found infected through intravenous drug use (IDU). About 4.5% of the patients were infected through homosexual route, while in 4.15% patients the cause of HIV infection was unidentified.

Table 3: Primary and secondary neurological illness observed in HIV positive patients.

Neurological Illness	*Types*	*(n=100) (%)*
Primary	Distal symmetric polyneuropathy (DSPN)	17
	AIDS dementia complex (ADC)	05
	Acute inflammatory demyelinating polyneuropathy	02
	Stroke syndromes	02
Secondary	Tuberculous bacterial meningitis	49
	Cryptococcal meningitis	16
	Toxoplasmosis	03
	Progressive multifocal leukoencephalopathy.	03
	neurosyphilis	06

Distal symmetrical polyneuropathy (DSPN) was found in 17% HIV patients. Cerebrovascular disease was detected in 7% of HIV infected individuals. Present study provided that tuberculous meningitis (TBM) as found in 49% of HIV patients and considered common secondary CNS illness in the present study, followed by cryptococcal meningitis (16%). Toxoplasmosis was observed in 3%, progressive multifocal leukoencephalopathy in 3% and neuro-syphilis in 6% of the cases. Three patient had herpes simplex encephalitis (presenting with altered sensorium and seizures with bilateral orbital and temporal lobe involvement) and 3 patients had cerebral toxoplasmosis which presented with right-sided partial seizure with secondary generalization. One patient had herpes zoster, affecting T4-t7 thoracic dermatome on the right side, presenting with radicular lancinating pain (Table-3).

HIV patients with CNS infections presented with low levels of CD4 counts i.e. <200/µL. The average CD4 count in cells/mm^3 in the presence of various clinical presentations was as follows: 170±100.9 in DSPN, 245.7±113.9 in AIDP, 120.3±81.8 in tuberculous meningitis, 41.0±29.60 incryptococcal meningitis, and 55.6±38.7 in toxoplasmosis (Table-4). In HIV-associated dementia (HAD), the mean CD4 count was 85±81.72. Statistically, there was no difference in the ART status and the development of neurological manifestations in HIV/AIDS patients.

Table 4: Mean CD4 count in neurological illness in HIV positive patients.

Neurological illness	*Mean CD4 Count ± Standard Deviation (SD)*
Tuberculous bacterial meningitis	120.3±81.8
Cryptococcal meningitis	41.0±29.60
Toxoplasmosis	55.6±38.7
Progressive multifocalLeucoencelopathy	115±75.5
Neurosyphilis	125±45.5
HIV-associated dementia (HAD)	85±81.72
Distal symmetric polyneuropathy	170±100.9
Acute inflammatory demyelinatingPolyneuropathy	245.7±113.9

Discussion

HIV-infected patients having CNS complication can be divided into meningitis, encephalopathy intracerebral space occupying lesions, and spinal cord process.[7] Where effective ART treatment implemented, these complications have declined markedly. As the age of HIV, the cognitive declines have been observed. In the hippocampus, basal ganglia, prefrontal cortex, and white matter slow neuro-degradation occur due to infected macrophages infiltrate the brain parenchyma. Release of IL-1, TNF, and IL-6 causes low damage to the CNS.[8]

In the present study, the age group 24-47 was found with high grade of neurological involvement, which correlates with a study done by Sircar et al.[9] The age group 24-27 is a highly productive section of our society put alarming effect in growth of a developing country.

Heterosexual transmission of HIV disease was also observed in this study. The study provided

similar pattern of results like studies from India and other Asian countries. While in Europe homosexual transmission is a commonest route.

In this study, ratio of male to female was 2:1, which is comparable to the study done by Soluet al and Sircar et al from India.[9,10] Tuberculous involvement was seen in 49 (49%) patients, out of which 09 had intracranial tuberculomas and 40 had tuberculous meningitis. This is similar to the findings of other studies in which the incidence of tuberculous involvement was 47% and 42%, respectively.[11,12] In tuberculous meningitis, common presenting symptoms were fever (55%) followed by headache (35%), altered consciousness (32%), and convulsions (12%).

It was observed that in United States, 5-10% patients had AIDS with cryptococcal meningitis the most common problem in HIV patients.[13] In present study, 16 out of 100 (16%) patients with neuro-AIDS had cryptococcal meningitis. The other symptoms like headache, fever and vomiting were the complaints in HIV patients with neurological manifestations. In HIV patients' Cryptococcal neoformans causes minimal inflammation with defused immune mechanism, which explains why neck rigidity and photophobia were infrequent in this study. Cryptococcal meningitis occurs in terminally ill patients with CD4 count <100 µL.[14] CSF examination of cryptococcal meningitis patients showed the average protein levels of 132%, sugar of 62%, and total cell of 45/mm^{-3} and lymphocytes of 95%. CSF cryptococcal antigen titer was used to diagnose in this study. Other studies documented the similar pattern of results as reported in previously.[15] The incidence of mortality due to cryptococcal meningitis in patients with HIV infection was reported in 45%. The poor prognostic predictors were altered mentation at the time of diagnosis, positive Indian ink staining, positive blood culture, a low CSF leukocyte count, high cryptococcal antigen titers, and increased CSF opening pressure. PML, Cryptococcal meningitis, toxoplasmosis and neurosyphilis reported were similar to the findings of two other studies by Abayomi et al and Rana at al.[16,17] In a Brazilian study and another by Deshpande et al., toxoplasmosis was considered main cause of CNS complication.[18,19] The most sensitive technique MRI was used to diagnose this entity. This infection generally occurred in HIV patients with low CD4 count.[20]

Progressive multifocal leuko encephalopathy (PML) was developing in 4% of AIDS patients, and it was main complication of AIDS in 25% of HIV cases. However, in the present study, 15 patients had such kind of history.

Neuro-syphilis a main complication and its association is not unexpected because both AIDS and neuro-syphilis are sexually transmitted diseases. But neuro-syphilis develop in late stages of disease.[21] Invasion of CNS by the organism Treponema palladium can also be expected to occur. Patients with neuro-syphilis had serum VDRL titers ≥1:16. The median of serum CD4 cell and VDRL l counts were 127cell/µL and 1:122 respectively.

HIV-associated myelopathy, neurocognitive impairment, myopathy, aseptic meningitis and peripheral neuropathy are primary illnesses. Another study revealed same kind of information as documented in this study.[22] Eight patients (8%) were diagnosed to be having a cerebrovascular accident (CVA). Five of them had an infarct in the basal ganglia and other three had an infarct in the cerebellum. CVA evidence provided in the present study is similar to that seen in another study.[23] DSPN is mostly seen in patients with low CD4 counts. DSPN is also the most common side-effects of ART. ADC was seen in 7% of our patients, which was diagnosed by the mini mental score examination (MMSE). Neuro-cognitive dysfunction generally occurred when less than 100 cell/µL CD4 count wasreported.[24]

Mean CD4 count (in cell/µL) in this study was 151±100.9 with DSPN, 259.7±113.9 with AIDP, 120.3±81.8 with TBM, 42.0±29.60 with cryptococcal meningitis, and 54.6±38.7 with toxoplasmosis. A study conducted by Deshpande from India was similar with this study.[25] In HAD, the mean CD4 count was 91 cells/µL, which is comparable with the NIMS study in which mean CD4 count was 92 cells/µL.[26] HIV patients with CD4 cell count below 200 are at a high risk of developing serious illnesses, which has been seen in this study too. The presence of neurological manifestations is associated with decreased CD4 counts. Cryptococcal meningitis was associated with lowest CD4 counts, and had a fatal outcome in 40% of the patients, followed by toxoplasmosis, HAD and neurosyphilis (Table-5). In KP Pakistan today, the only affordable methodology is the estimation of the CD4 cell counts. It can serve as a guide to assess the HIV status, assess the risk for the development of neurological manifestations in such patients and help in instituting timely intervention in the form of prophylaxis and treatment.[27] The mortality was 25% in TBM, 15% in toxoplasmosis and 40% in cryptococcal meningitis (Table-4). In the era of HAART and specific treatment that is available for opportunistic infections, mortality in patients with HIV with neurological illness has considerably decreased. Lady Reading hospital, being KP biggest territory hospital most patients of HIV/AIDS are referred for treatment and management. The study provided useful information that neurological problems should be identified and

treated at early stage of HIV to decrease the morbidity and mortality.

The reported CNS opportunistic infections in HIV patients in this study provided the need of intervention on neurological manifestation in HIV patients. A proper guideline of treatment and diagnosis of CNS manifestation should be a part of ART treatment. Awareness is needed among health professionals regarding neurological manifestation among HIV patients to address the issue before entering HIV patient in a terminal stage of diseases.

Acknowledgement

The Authors are grateful to the staffs of Lady reading hospital, HIV center Hayatabad medical complex and PHRC Research Center Khyber Medical University for their consent to carry out this research and their timely support.

Conflict of interest: None declared.

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