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Central Nervous System Infections in HIV Patients: An Experience from a Tertiary Level Hospital in Mumbai.

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ABSTRACT

Background: Opportunistic infections of the central nervous system (CNS) are common complications of advanced immunodeficiency in individuals with human immunodeficiency virus (HIV) infection. We aimed to study the clinical profile of CNS infections in HIV patients, effect of antiretroviral therapy (ART) on various patient variables and mortality outcomes associated with various patient characteristics. **Methods:** After approval of the ethics committee, we enrolled 100 patients from the Department of Medicine at Lokmanya Tilak Municipal General Hospital from January 2011. Patients who were diagnosed with HIV using ELISA and admitted with a CMS infection were consented and enrolled for the study. Various clinico-laboratory parameters like CD4 counts, ART, signs and symptoms were collected and analysed with approapriate statistical techniques. P vlaue less than 0.05 was taken as staistically significant. **Results:** Out of 100 patients, 71 were males, average age 35.24 years. Majority had headaches, CD4 counts between 101-200 cells/mm3and 57 were on ART. Tubercular mengitis was the most common CNS infection in our patient population. We found statistical signifiance in the occurance of CNS infections and ART among patients. Mortality outcomes were significantly associated with signs and symptoms of the patients ($p < 0.05$). **Conclusion:** Our results show that CNS infections can occur even with high CD4 counts. So strict monitoring and long term followup of HIV patients is needed. Areas of future research should focus on long term clinical outcomes of HIV patients and elucidating factors reponsible for it.

Keywords: HIV, central nervous system, infection, correlation, CD4 counts.

INTRODUCTION

Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes acquired immunodeficiency syndrome (AIDS), a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. HIV infects vital cells in the human immune system such as helper T cells (specifically CD4+ T cells), macrophages, and dendritic cells. When CD4+ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections.[1] Opportunistic infections of the central nervous system (CNS) are common complications of advanced immunodeficiency in individuals with human immunodeficiency virus infection. Prompt diagnosis and treatment of such disorders is critical. Also, in the era of highly active antiretroviral therapy (HAART), these disease states have changed in presentation and epidemiology.[2] Diseases of the central nervous system (CNS) in patients infected with the human immunodeficiency virus (HIV) result directly from HIV itself or from a variety of opportunistic agents. These infections include tuberculosis, cryptococcosis, toxoplasmosis, progressive multifocal leukoencephalopathy and others.

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CD4 cells are white blood cells that play important roles in the immune system. Even while a person with HIV feels well and has no symptoms, large no of CD4 cells are infected by HIV and are destroyed each day, and large no of CD4 cells are produced to replace them. The CD4 T-cell count is a reliable indicator of the current risk of acquiring opportunistic infections. Antiretroviral treatment can slow the course of the disease and may lead to a near-normal life expectancy. Highly active antiretroviral therapy (HAART) is the principal method for preventing immune deterioration. In

addition, prophylaxis for specific opportunistic infections is indicated in particular cases. In this study we aimed to study clinical profile of CNS infections in HIV patients and the correlation of CNS infections in HIV patients and CD4 counts. We also studied the difference in profile of CNS infections in HIV patients on antiretroviral therapy (ART) compared to those that not on antiretroviral therapy (ART). Finally we wanted to study association of comorbidities with outcome in HIV patients with CNS infections.

MATERIALS AND METHODS

Study Design and Patient population

This observational cross-section study was designed at Lokmanya Tilak Municipal General Hospital. Data would be collected over a period of 18 months, starting January 2011. Based on the number of HIV patients admitted at our hospital in previous years, we decided to include 100 pateints admitted in medicine ward during the study period. Patients fulfiling our inclusion and exlusion creiteria were included in the study. Before commencing on the study we will get approval from the Institutional Ethics Committee. Patient giving written,informed and valid consent will be taken in the study. If patient is found in altered or unconscious state then consent will be taken from legal authorized person. We will include HIV positive patients, 12 years or above, who have been confirmed by ELISA method and were admitted with central nervous system infection. We will exclude those HIV patients who refused to give a written consent.

Data Collection and Data Analaysis

After enrolling the patient we will obtain demographic information of the patient. Along with that all relevant medical history will be obtained, either from the medical records or patient themselves. We will note histpry regarding headache, altered sensorium, seizure, stroke, dementia or any features suggestive of raised intracranial tension. We will also obtain history suggestive of common comorbidities like pulmonary tuberculosis (TB), disseminated TB, liver dysfunction and alcohol abuse. During the course of the study we will obtain routine hematological investigations for all the patients. Additionally, we will obtain CD4 Counts, CSF routine microscopy, CSF Adenosine Deaminase, CSF (India ink preparation) for Cryptococcus, IgG Toxoplasma, Fundus Examination, CT Brain scan, MRI Brain and CSF Fungal culture for all patients. The patients will be observed for the period of indoor admission period. All the collected data will be entered in Microsoft excel sheet and imported in to Statistical Package for Social Sciences (SPSS) version 16 for statistical analalysis. Appropriate statistical tests will be used to study the difference in the clinical outcome of patients who were treated with HAART with those who were not (p value less than 0.05 was taken as statistically significant). Correlation statistics were used to find the correlation of CNS infections and CD4 counts.

RESULTS

In our study 56% of patients had Tuberculous meningitis, 11% patients had Tuberculoma, 11% patients had Cryptococcal meningitis and 13% had Toxoplasmosis, 5% patients had progressive multifocal leucoencephalopathy (PML) and 3% patients had HIV encephalopathy and 2% had CMV encephalitis [Table 1]. The mean age for patients on ART was 34.37years compared to those not on ART was 36.40 years [Table 2]. The mean CD4 counts in patients on ART was 194.19±96.45 cells/mm3compared to 221.23±229.00 cells/mm3 those not on ART. The signs and symptoms were also not comparable in the above 2 groups. Similarly there was no significant difference in the incidence of CNS infections except tuberculoma in the 2 groups. There was no statistically significant difference in mortality in patients of CNS infection in HIV in those on ART verses those not on ART [Table 3]. 8 patients (14%) die on ART compared to 10 patients (23.3%) who are not on ART. Thus in our study we did not find significant difference except few in the two groups, patients those on ART verses those not on ART.

DISCUSSION

This cross sectional observational study was carried out in a tertiary care hospital. In this study 100 HIV positive patients with neurological involvement were involved, of which 71% patients were males. Gongora Rivera F et al in their study found 89.3% males and 10.7% female patients.[3] Attili Venkata Satya et al found that males were higher in number than females.[4] Mean age of all patients was 35.24 years. In our study 87% patients were aware of their HIV positive status at the time of admission for neurological symptoms; whereas 13% were diagnosed on admission i.e. their first presentationwas a neurological involvement.[5] Vijay D Teja et al found that only 9.25% of their patients were aware of their HIV positive status at the time of admission for neurological involvement. Thus large proportion of our patient population knew their HIV status in our study group. Jowi et al had studied 150 HIV patients with neurological involvement; CD4 count was available in 72 patients.[6] Patients with encephalitis had mean CD4 count of 82, patients with cerebral toxoplasmosis had mean CD4 count of 59 cells, patients with focal neurological deficit had mean CD4 count of 120 cells, tuberculous meningitis patients had mean CD4 count of 67 cells. Thus in our study mean CD4 count was significantly

low in all neurological manifestations suggesting immunosuppression. This is consistent with the study of relationship between several neurological complications and CD4 count by Gochitashvili N et al.[7]

Table 1: Baseline characteristics of patients included in the study.

Total number of patients	100
Average age	35.24 ± 7.92 years
Males	71
Signs and symptoms	
Headache	83
Altered sensorium	72
Seizure	37
Stroke	3
Dementia	4
Raised intracranial tension	5
Patients on Anti-retroviral therapy	57
CD4 counts (cells/mm^3)	
<100	18
101-200	39
201-300	22
>300	17
Opportunistic infection diagnosis	
CMV* Encephalitis	2
Cryptococcus Meningitis	11
HIV Encephalopathy	3
Progressive multifocal leukoencephalopathy	5
Tubercular Meningitis	56
Toxoplasmosis	13
Tuberculosis	10

* CMV: Cytomegalovirus

Table 2: Correlation of anti-retroviral therapy with variates.

Variable	ART* patients	Non-ART patients	p value
n	57	43	>0.05
Mean age	34.37 ± 37	36.40 ± 8.17	
Males	40	31	
Signs and Symptoms			
Headache	48	35	>0.05
Altered sensorium	39	33	
Seizure	24	13	
Stroke	1	2	
Dementia	2	2	
Raised intracranial tension	3	2	
CD4 counts			
<100	8	10	>0.05
101-200	25	14	
201-300	13	9	
>300	11	6	
Opportunistic infection diagnosis			
CMV# Encephalitis	1	1	<0.05
Cryptococcus Meningitis	6	5	
HIV Encephalopathy	1	2	
Progressive multifocal leukoencephalopathy	4	1	
Tubercular Meningitis	30	26	
Toxoplasmosis	6	7	
Tuberculosis	9	1	

*ART: Anti-retroviral therapy
#CMV: Cytomegalovirus

Table 3: Correlation of mortality outcomes with variates.

Variable	Dead patients	Survived patients	p value
Antiretroviral therapy			
Yes	8	49	>0.05
No	10	33	
Signs and symptoms			
Headache	18	65	<0.05
Altered sensorium	18	54	
Seizure	6	31	
Stroke	2	1	
Dementia	1	3	
Raised intracranial tension	4	1	

We could not observe any statistical difference in mortality in patients those on ART (14%) verses those not on ART (23.3%). Mortality was more in patients those presented with headache, altered sensorium and seizures. Despite the limited diagnostic capabilities, important co-morbid conditions observed can impact future HIV treatment success. Tuberculosis was the most common inpatient diagnosis and the most common cause of death, with extra-pulmonary cases outnumbering pulmonary. TB accounts for more than 50 per cent of deaths among HIV-infected persons in India.[8] Given the high rates of TB-HIV coinfection and the significant morbidity and mortality associated with it, effective HIV treatment measures will need to improve early TB detection and management. Interestingly, alcoholic liver disease was a common discharge diagnosis for HIV-infected individuals. The existence of alcohol abuse in the setting of HIV deserves special attention given its potential to decrease HIV treatment adherence, weaken the nutritional status of the individual, and increase the risk of adverse events from antituberculosis therapy and ART.[9]

In our study there were 56 patients of Tuberculous meningitis most of them presented with fever and headache. Altered sensorium and focal neurological deficit were also present in few patients. In a study conducted by Attili Suresh Venkata Satya et al in 2006 found that 87.5% patients of Tuberculous Meningitis presented with headache, 75% of patients had fever as the presenting symptom.[4] All the Toxoplasmosis patients (13) (100%)in our study presented with seizures, 9 patients also had history of headache. Six patients were on ART. Most of the patients had CD4 count in the range of 100-200. In a study conducted by Attili Suresh Venkata Satya et al in 2006 found that all toxoplasmosis patients had focal neurological deficit as a presenting complaint.[4]

We found 3 patients had HIV encephalopathy, diagnosed on history and MRI findings. All patients had dementia as the presenting complaint. CD4 counts were in 50-150 range. Reports about AIDS dementia complex (ADC) in India are minimal. Review of literature revealed one study in Jaipur of 30 AIDS patients, 4 of whom were diagnosed with ADC.[10] HAART has led to a decrease in systemic

opportunistic infections in HIV infection. The incidence of CNS opportunistic infections has also decreased significantly. The incidence of cryptococcal meningitis has decreased in the Multicenter AIDS Cohort Study (MACS) since the introduction of HAART in 1996.[11] For CNS toxoplasmosis, in the Multicenter AIDS Cohort Study (MACS), there was a trend for a decreased incidence since the introductionof HAART.[11] Similarly, at the Johns Hopkins HIV clinic, there has been a significant decrease in the incidence of toxoplasmosis since the introduction of HAART.[12] Thus in our study we did not find significant difference except few in the two groups, patients those on ART verses those not on ART. Probably large cohort study and long term follow up is needed. Our study has some limitations. Study population was small compared to the high incidence and prevalence of the disease and patients were only followed up till the hospital admission period. Additionally, only outcome in few comorbid conditions was studied.

CONCLUSION

In the HAART era, though CNS infections in HIV patients are more common with very low CD4 counts, but they can occur at relatively high CD4 counts also. So monitoring and follow up is required in those cases to prevent subsequent morbidity and mortality. Co-morbidities were associated with poorer prognosis. In studied comorbidities, maximum mortality was seen in patients with disseminated tuberculosis followed by liver dysfunction followed by extra CNS tuberculosis and least mortality was seen with alcohol consumption.

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