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Study Of Tuberculosis And Cryptococcal Meningitis In Hiv Infected Patients And Their Correlation With Cd4 Count

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ABSTRACT

Aim To study clinical and CSF profile of Tubercular and Cryptococcal meningitis in HIV infected hospitalised patients and to correlate clinical profile with CD-4 count.

Methodology All the admitted HIV positive patients whose clinical manifestations were suggestive of meningitis, were screened by CSF analysis and specific diagnosis made according to CSF findings. CSF-AFB stain, CSF cultur , and india ink preparation were also done to make the diagnosis more accurate. CD-4 count of every HIV sereopositive meningitis patients was determined using flow-cytometry

Results In our study, thirty seven meningitis patients were HIV positive. Patient's age ranges from 20-70 years. We found only two types of meningitis in our study- Tubercular meningitis and Cyptococcal meningitis. 81.08% of patients had Tubercular meningitis and 18.91% of patients had Cyptococcal meningitis in our study. Tubercular meningitis was significantly more common than Cryptococcal meningitis.

Conclusion HIV infected patients are at high risk for opportunistic infections including meningeal involvement. Severe manifestations of meningitis keeps on increasing with decrease in CD-4 count. By early diagnosis and management of HIV positive patients with HAART-Highly Active Anti Retroviral Therapy we can keep CD-4 count of patient elevated to prevalent TB meningitis and Cryptococcal meningitis and also the sequel of disease.

KEYWORDS :

INTRODUCTION:

AIDS, the acquired immunodeficiency syndrome is fatal illness caused by a retrovirus known as human immunodeficiency virus (HIV) which breaks down the body's immune system, leaving the victim venerable to a host of life threatening opportunistic infection, neurological disorder or unusual malignancies. AIDS was first recognized in the United States in the summer of 1981 in homosexual man. The disease was soon recognized in male and female injection drug users in haemophiliacs and blood transfusion recipients, among female sexual partners of men with AIDS; and among infants born to mothers with AIDS. The first case of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in India was detected in 1986 in the state of Tamilnadu and since then the spread of HIV/AIDS across the nation has been relentless. [1, 2]

Cases have been reported from all states and union territories of India. Though the overall prevalence of HIV infection is low (<1%), the total number of cases is high. As per estimates, by the end of 2002, about 4.58 million adults were infected with HIV Even more ominous has been the shift of the epidemic from high-risk groups such as injectable drug users (IDU) and patients with other sexually transmitted diseases, to low-risk groups like married, monogamous women [3].

Though the majority of HIV-infected population lives in developing nations, there is a paucity of data on natural history, pattern of disease and survival of hospitalised patients with HIV/AIDS from these regions, especially India. It is well established that manifestations of AIDS are influenced by factors such as endemic infections and malnutrition that are widely prevalent in these regions. Conventional disease staging criteria, which were developed in western populations may not hold well in these settings. Added to this, resource constraints prohibit evaluation and decision-making based on cost and labor-intensive methods such as CD4+ cell counts and viral RNA load estimation. Timely initiation of prophylaxis for opportunistic infections (OIs) and their prompt recognition and treatment are the only economically viable options. In this scenario, knowledge regarding the pattern of OIs, will be useful. This study was conducted to elucidate the frequency of various OIs and non-infectious opportunistic conditions in hospitalized HIV-infected patients, from north India.

Once infected with HIV, the progression to AIDS to premature death is the reality for people in most poor countries. We have a lot of challenges posted by HIV/AIDS. Till now HIV/AIDS has no complete cure or preventive/therapeutic vaccine. Disease has insidious nature and its major manifestations occur only at later stages leading to its late diagnosis and poor reactive response. [3]

Neurological disorders complicate HIV infection in 30% to 40% of patients, and any part of the neuraxis may be affected. Early CNS infection is usually asymptomatic or responsible for rare disorders such as acute aseptic meningitis or encephalitis. During the later stages of infection both the major CNS opportunistic infection and AIDS dementia complex develop. [4]

Antiretroviral therapy has decreased morbidity and mortality in HIV infected patients with advanced disease. Incidence rates of neurological manifestations such as HIV associated neuropsychological impairment and opportunistic infection seem to have declined. HIV infections in tropical countries could kill patients before the other neurological manifestations have the time to develop. In these countries, three treatable opportunistic infections namely, cryptococcal meningitis, toxoplasmosis, and tuberculosis cause most of the morbidity and mortality. [5]

Meningitis in patients with HIV infection is mostly infection in origin. Two opportunistic pathogens stand out as important neurological problem in patients with AIDS – Cryptococcus neoformans and Mycobacterium tuberculosis, and together they account for most of the cases of meningitis. In our study, we will throw some more light in profile of meningitis in HIV patients which will help its early and better management in future. [6]

MATERIAL AND METHOD

The study was conducted in the Department of Medicine at Gandhi Medical College and Hamidia Hospital Bhopal. The study subject were selected from HIV positive patients admitted to medicine wards.

Study population The study population consisted of all the HIV positive adult patients with clinical and laboratory diagnosis of Meningitis.

Type of Study Observational Cross-Sectional Study.

Inclusion Criteria

- HIV infected patients presenting with manifestations indicative of Meningitis (eg. Fever headache, neck stiffness, vomiting, photophobia altered level of consciousness etc), confirmed in CSF study to be a case of meningitis
- Patients with clinical diagnosis of meningitis, confirmed in CSF study to be a case of meningitis who were incidentally found to be HIV positive.

Exclusion Criteria

- HIV infected patient with neurological disease other than meningitis.
- HIV infected meningitis patients who is also suffering from some other neurological illness.
- Meningitis patients not suffering from HIV infection.

Comparison Group

Thirty tubercular meningitis patients not having HIV infection were taken as comparison group to compare clinical and CSF characteristics of TBM patients with and without HIV infection.

METHOD:

All the admitted HIV positive patients whose clinical manifestations were suggestive of meningitis, were screened by CSF analysis and specific diagnostic made according to CSF findings. CSF-ADA, CSF-AFB stain, CSF culture , and india ink preparation were also done to make the diagnosis more accurate. CD-4 count of every HIV sereopositive meningitis patients was determined using flow-cytometry.

Data was collected in a preset proforma to meet the objective of study. A detailed history, physical examination including thorough neurological examination and necessary investigations were recorded.

Investigation

- CBP with ESR.
- HIV testing by ELISA test done in ICTC (integrated counseling and testing centre) GMC Bhopal as per NACO guideline.
- CD-4 count by Flow cytometry
- CSF analysis-protein, glucose, cell count and type, Culture, AFB, ADA, Gram stain, India ink preparation.
- Chest X-Ray.
- Neuroimaging (CT/MRI) where required.

Out study is observational cross-sectional study, no active procedure was done by us. Diagnosed meningitis patients who were HIV positive or incidentally diagnosed to be HIV positive, were included in study.

Examination of the CSF begins immediately after collection of the specimen. The fluid is observed for turbidity; normal fluid is clear. The colour of the fluid is noted next. This must be done within 30 minutes of collection of the fluid, since red cell lysis after his time can affect the results. This is a vital piece of information that often provides the sole objective clue to the diagnosis of subarachnoid hemorrhage. A gram stain, AFB (acid-fast bacillus) stain for tuberculosis, and India ink examination should be done promptly on the CSF.

The India ink examination has the charm of an immediate, specific diagnosis of cryptococcal meningitis within minutes of obtaining CSF. Unfortunately it is positive in only 50% of cases of cryptococcal meningitis (up to 80% in AIDS patients).

OBSERVATION:

TABLE-1 DISTRIBUTION OF MENINGITIS IN HIV POSITIVE PATIENTS

Diagnosis	Frequency	Percent
Tubercular meningitis	30	81.08
Cryptococcal meningitis	7	18.91

Tubercular meningitis is more common than Cryptococcal meningitis in HIV positive patients.

TABLE -2 CLINICAL MANIFESTATIONS OF MENINGITIS IN HIV POSITIVE PATIENTS

Symptoms	TBM (HIV positive)		Crytococcal Meningitis	
	Frequency	Percent	Frequency	Percent
Fever	30	100	7	100
Headache	28	93.33	6	85.71
Vomiting	22	73.33	5	71.43
Neck Stiffness	21	70	4	57.14
Altered sensorium	21	70	3	42.86
Convulsion	10	33.33	2	28.57
FND	10	33.33	1	14.29

FND – Focal Neurological Deficit; TBM- Tubercular Meningitis.

Fever is present in all the patients of Tubercular and Cryptococcal Meningitis. Headache is second most common symptom in both Tubercular Meningitis (93.33%) and Cryptococcal Meningitis (85.71%). Vomitting and Neck stiffness are other common symptoms both in Tubercular Meningitis and Cryptococcal Meningitis.

TABLE -3 CATEGORISATION OF CD-4 COUNT IN HIV POSITIVE MENINGITIS

COUNT	FREQUENCY	PERCENTAGE
<50	6	16.21
50-100	8	21.62
101-200	23	62.16
>200	0	0
Total	37	100

- Most of the Meningitis patients are in CD-4 range of 101-200.
- Second most common range in 50-100.

TABLE-4 CATEGORISATION OF CD-4 COUNT IN DIFFERENT SUBTYPES OF MENINGITIS

CD-4 Count	Tubercular Meningitis (HIV positive)		Cryptococcal Meningitis (HIV)positive	
	Frequency	Percentage	Frequency	Percentage
<50	1	3.33	5	71.43
50-100	7	23.33	1	14.29
101-200	22	73.33	1	14.29
>200	0	0	0	0

CHI SQ= 19.6 P Value<0.0001

- Most of the tubercular Meningitis patients (73.33%0 are in CD-4 range of 101-200.

- Most of the Cryptococcal Meningitis patients (71.43%) are in CD-4 range of <50.
- NO TBM or Cryptococcam Meningitis patients stand in CD-4 range of >200.

TABLE:-5 ASSOCIATION OF CD-4 COUNT WITH SEVERE MANIFESTATION OF TUBERCULAR MENINGITIS (HIV POSITIVE)

CD-4 Count	Altered Consciousness		Convulsion		FND	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
>200	0	0	0	0	0	0
100-200	12	40	3	10	1	3.3
<100	6	20	5	16.67	6	20

CHI SQ=6.05 P=0.049

Frequency of severe manifestation of Tubercular Meningitis increase with decreasing CD-4 count.

RESULT

In our study, thirty seven meningitis patients were HIV positive. Patient's age ranges from 20-70 years. Male patients (78.38%) are more than female patients (21.6%). Male to female sex ratio is 3.6:1.We found only two types of meningitis in our study- Tubercular meningitis and Cyptococcal meningitis. 81.08% of patients had Tubercular meningitis and 18.91% of patients had Cyptococcal meningitis in our study. Tubercular meningitis was significantly more common than Cryptococcal meningitis.

Common clinical manifestations of HIV positive Tubercular meningitis patients were not significantly different (P>0.05) than HIV negative Tubercular meningitis patients. Severe clinical manifestations of meningitis (Altered consciousness, Convulsion, Focal neurological deficit) were significantly more common (P<0.05) in HIV positive Tubercular meningitis patients. Mean CSF-ADA was 15.28 and most of the Tubercular meningitis patients had ADA>10 U/L. Only 10% of TBM patients had CSF-ADA<8 U/L.

CSF profile of HIV positive Tubercular meningitis patients is not significantly different (p>0.05) than in HIV negative Tubercular meningitis patients. Most of the Meningitis patients in our study were in CD-4 range of 101-200.Most of the Tubercular Meningitis patients (73.33%) are in CD-4 rage of 101-200.Most of the Cryptococcal Meningitis patients (71.43%) are in CD-4 range of <50 (P<0.0001).No TBM of Cryptococcal Meningitis patients was found in CD-4 range of >200.Frequency of severe manifestation (Altered consciousness, Convulsion, Focal neurological deficit) is more with decreasing CD-4 count both in Tubercular and Cyptococcal meningitis (P<0.05).

Statistical Analysis

Data was analyzed using SPSS 20 statistical package. A descriptive analysis was done on all variables to obtain a frequency distribution. The mean + SD and ranges were calculated for quantitative variables. Continuous variables were compared by the Student t test. Proportions were analyzed with the chi-square test. A P value of 0.05 or less was considered statistically significant.

DISCUSSION:-

In the present study, 37 patients fulfilled the inclusion criteria of HIV seopositivity with Meningitis (Tubercular or Cryptococcal) during study period from JAN 2013-DEC-2013. Thirty age and sex matched Tubercular Meningitis patients who were HIV negative were chosen to compare clinical profile and CSF profile to Tubercular Meningitis in HIV and non HIV infected patients.

Similar observations were made by Crowe SM, Carlin JB et al who studied that Infection with the human immunodeficiency virus (HIV) results in progressive depletion of the CD4 subset T-lymphocytes and the development of opportunistic infections and certain malignancies. Significant differences in CD4 lymphocyte numbers were observed between the 12 ADIs, oral candidiasis, and asymptomatic infection, allowing them to be grouped into five general categories, based on mean CD4 count. Their data concur with clinical impressions and provided a basis for interim treatment and prophylaxis recommendations.[7]

Literature on the spectrum of opportunistic disease in human immunodeficiency virus (HIV)-infected patients from developing countries is sparse. Sharma SK et al therefore did a study .The objective of this study was to document the spectrum and determine the frequency of various opportunistic infections (OIs) and non-infectious opportunistic diseases, in hospitalized HIV-infected patients from north India. One hundred and thirty five consecutive, HIV-infected patients (age 34 ± 10 years, females 17%) admitted to a tertiary care hospital in north India, for the evaluation and management of an OI or HIV-related disorder between January 2000 and July 2003, were studied. They concluded that a wide spectrum of disease, including both OIs and non-infectious opportunistic diseases, is seen in hospitalised HIV-infected patients from north India. Tuberculosis remains the most common OI and is the commonest cause of death in these patients. [8]

In studies of French N, Gray K et al cryptococcal disease was diagnosed in 77 individuals (rate 40.4/1000 person-years) and was associated with 17% of all deaths. Risk of infection was strongly associated with CD4 T cell counts < 200 × 106 cells. Meningism was present infrequently on presentation (18%). Clinical findings had limited discriminatory diagnostic value. Serum cryptococcal antigen testing was the most sensitive and robust diagnostic test. Cryptococcal antigenaemia preceded symptoms by a median of 22 days (> 100 days in 11% of patients). Survival following diagnosis was poor (median survival 26 days; range 0–138). So they concluded that cryptococcal infection is an important contributor to mortality and suffering in HIV-infected Ugandans. Improvements in access to effective therapy of established disease are necessary. In addition, prevention strategies, in particular chemoprophylaxis, should be evaluated while awaiting the outcome of initiatives to make antiretroviral therapy more widely available.[9]

Jarvis JN et al did an evaluation of a novel point-of-care cryptococcal antigen test on serum, plasma, and urine from patients with HIV-associated cryptococcal meningitis. They compared cryptococcal antigen (CRAG) concentrations in plasma, serum, and urine from patients with CM, using an antigen-capture assay for glucuronoxylomannan (GXM) and a novel POC dipstick test. It was concluded that this novel dipstick test has the potential to markedly improve early diagnosis of CM in many settings, enabling testing of urine in patients presenting to health care facilities in which lumbar puncture, or even blood sampling, is not feasible.[10]

Dubé MP et al WHO characterized the symptoms, signs, laboratory findings, and outcome of culture-proven meningitis due to Mycobacterium tuberculosis in patients with and without human immunodeficiency virus (HIV) infection. With the exception of an increased incidence of intracerebral mass lesions in HIV-infected individuals, HIV infection appears to have little impact on the findings and in-hospital mortality of tuberculous meningitis. [11]

Moore RD did a retrospective and prospective observational study. They did a study on 1246 HIV-infected patients with CD4+ counts of 300 cells/mm3 or less. Incidence rates and Kaplan-Meier estimates of the probability of developing opportunistic disease with time, distribution of the CD4+ counts at which opportunistic disease develops, survival after the development of opportunistic disease, and the association between preventive drug therapies and the occurrence of opportunistic infection.. They concluded that continued efforts are needed to develop effective strategies for preventing opportunistic disease in very advanced HIV infection. Results were similar to our studies.[12]

CONCLUSION

HIV infected patients are at high risk for opportunistic infections including meningeal involvement. With this fact in mind the study was conducted to understand clinical profile of meningitis in this group of patients. In our study, most common type of meningitis in HIV positive patients came out to be Tubercular Meningitis followed by Cryptococcal Meningitis. Severe manifestations become common as CD4 count declines.

We conclude that by early diagnosis and management of HIV positive patients with HAART- Highly Active Anti Retroviral Therapy we can keep CD-4 count of patient elevated to prevalent TB meningitis and Cryptococcal meningitis and also the sequel of disease.

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