JMSCR Vol||06||Issue||12||Page 1016-1021||December 2018

www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v6i12.165

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Clinico Radiological Profile of HIV Positive TBM Patients and Its Correlation with CD4 Count

Authors
Dr Manoj Kumar[1], Dr Tejpal Singh[2*], Dr Faisal Zia[3], Dr Awadhesh Yadav[4] Dr Kushal Pal[5]
[1]Senior Consultant
[2]Professor, Dept of Medicine, SN Medical College, Agra
[3,4,5]Junior Resident, PG Dept Medicine , S N Medical college Agra, India
*Corresponding Author
Dr Tejpal Singh
Email: *drtejpal.singh@yahoo.com*, Mob: 9897487984

Abstract
Background & Aim: *HIV infected persons are at risk of developing disseminated forms of TB, such as tuberculous meningitis (TBM). As the HIV infection primarily impairs the cell mediated immunity (CMI), the immune responses to TB bacilli seen in HIC infected may be different and may manifest in different clinical, radiological and CSF findings. Moreover as the immunity varies with CD4 count, there could be differences in clinico-radiological features at different CD4 counts. The present study was conducted to assess the clinical, CSF and radiological features of TBM in HIV positives and to study its relation with CD4 count.*
Materials and Methods: *Clinical, radiological and CSF features of 100 HIV positive TBM patients were studied and its relation with CD4 count was analyzed.*
Results: *The findings are notable by the difference in radiological findings between different CD4 count groups. Basal meningeal enhancement and hydrocephalus was conspicuously less common in those with CD4 count less than 50. Radiological findings are also remarkable by the presence of normal radiological findings in a sizeable proportion of patients with low CD4 count. CSF protein and total cell count is significantly less in those with CD4 count less than 50.*
Conclusion: *Like tuberculosis of other organs (notably lung), clinical, CSF and radiological findings in HIV patients can be quite different especially in those with severe immunosuppression. Therefore, a high degree of suspicion is required when interpreting radiological and CSF findings of HIV positive TBM patients.*
Keywords: *HIV, TBM, CD4 Count.*

Introduction

Tuberculosis (TB) and HIV have been closely linked since the emergence of AIDS.[1] Worldwide, TB is the most common opportunistic infection affecting HIV seropositive individuals,[2] and it remains the most common cause of death in patients with AIDS.[3] In 2016, t here were an estimated 1.3 million TB deaths among HIV-negative people and an additional 374000 deaths among HIV positive people.

HIV-infected persons may present with unusual clinical features of TB, and are at risk of developing disseminated forms of TB, such as tuberculous meningitis (TBM). Cell mediated immunity (CMI) plays a major role in limiting the spread of tubercle bacilli within the body and many pathological features of TBM are the result of cellular immune responses to the presence of the tubercle bacilli in the subarachnoid space. As the HIV infection primarily impairs the CMI, the immune responses to TB bacilli seen in HIV infected may be different and hence the pathological features seen in HIV positive patients may be very different from those seen in patients with relatively normal CMI, these different from those seen in patients with relatively normal CMI. These different features may be reflected in clinical and radiological features. Although such differences have been demonstrated in pulmonary and abdominal tuberculosis in HIV-P patients.[4,5] There is scarcity of studies showing such differences in TBM patients. Moreover as the immunity varies with CD4 count, there could be differences in clinico-radiological features at different CD4 counts.

The objective of the present study was to assess the clinical, CSF and radiological features of TBM in HIC positive.

Material & Methods

This was a prospective observational study conducted at Sarojini Naidu Medical College, Agra which is one of the largest tertiary care centre of Uttar Pradesh, India and the referral hospital for ART run under the aegis of the National AIDS Control Organization (NACO). In total 100 patients were studied from August, 2009 to July, 2010. All previously diagnosed & newly diagnosed patients of TBM with HIV co-infection attending the OPD and admitted in wards were included in the study after taking written informed consent. Patients with other types of bacterial, viral and fungal meningitis were excluded from the study. Patients with history of other neurological disease, alcohol and other drug abuses like narcotics, sedatives and hypnotics were excluded from the study. Detailed clinical history with special emphasis on consciousness convulsions and headache was taken. Thorough higher mental functions, sensory, motor and cranial nerve examination were done. Apart from routine investigations, CD4 count was measured by standard flow cytometry method. CSF examination was done. CT head or MRI brain was done in all patients. Other diagnostic investigation like toxoplasma serology and electrophysiological studies were done wherever required.

Tuberculous meningitis was diagnosed if Mycobacterium tuberculosis was isolated in the CSF. In the absence of definitive microbiologic evidence, tuberculous meningitis was diagnosed based on neurological findings in combination with typical CSF alterations (lymphocytic predominance, raised protein, reduced glucose), with exclusion of other aetiologies. The neurological status of patients was classified according to the Modified British Medical Research Council (BMRC) staging system which has been shown to have considerable prognostic value. In this modified BMRC staging, patients meet criteria for stage 1 disease, if they are alert and oriented, without a neurological deficit. Patients with stage 2 disease have a focal neurological sign or Glasgow coma score from 10-14 (with or without neurological deficit). In stage 3 disease patients have a score less than 10.[6]

Patients were also classified based on CD4 counts into 3 groups: Group A with CD4 count < 50, Group B with CD4 Count - 50 - 200 and Group C with CD4 count > 200.

The Clinical, radiological & CSF features and their relation with the CD4 count was analyzed statistically. Simple tabular analysis with percentage was used to draw the inferences in the present study. Besides this, single factor ANOVA and F-test were used wherever relevant to analyse.

Result

The study was carried out in 100 HIV positive TBM patients. Most of the patients 993 patients)

belonged to the age group of 30 to 59 and majority of patients were males (Male = 78 Vs. Females = 22). Distribution of patients according to CD4 count and BMRC stage is give in table 1. In our hospital, mot patients present in advanced stage of disease. Thus, only 5 patients belonged to stage 1.

Table 1 Distribution of patients according to CD4 count & BMRC stages

CD4 Count Groups	% of Patients
Group A (CD4 count < 50)	43
Group B (CD4 count 50 - 200)	34
Group C (CD4 count > 200)	23
BMRC Stages	
Stage 1	5
Stage 2	40
Stage	55

Clinical Features (Fig. 1)

Frequency of clinical features according to CD4 count is given in table. Fever is the most common symptom closely followed by headache and nausea / vomiting. Moreover, clinical findings were relatively similar between the groups.

Fig. 1 : Clinical findings in HIV positive TBM patients

Radiological findings (Table -2)

Radiological findings according to CD4 count groups are given in Table 2. The findings are conspicuous by the difference in radiological findings between different CD4 count groups. Baal meningeal enhancement and hydrocephalus was conspicuously less common in those with the CD4 count less than 50. Radiological findings are also remarkable by the presence of normal radiological finding in a sizeable proportion of patients with low CD4 count (Normal radiological findings in Group A = 30.23%, Group B = 11.76% and Group C = 0%).

Table 2: Radiological findings in HIV positive TBM patients

Radiological Findings	% of Patients			
	Group A (CD4 Count <50)	Group B (CD4 Count 50 - 200)	Group C (CD4 Count > 200)	Total
Normal	30.23	11.76	0	17
Tuberculoma	11.63	17.65	17.39	15
Basal meningeal enhancement	9.30	70.59	82.61	47
Hydrocephalus	9.30	58.82	39.13	33
Infarct	23.26	26.47	17.39	23
Cerebral Atrophy	51.16	26.47	0.00	31

CSF findings (Table 3)

CSF findings are given in table 3. CSF protein and total cell count is significant less in those with CD4 count less than 50 ($p < 0.0001$ for both), but CF glucose and ADA levels were similar between the groups. Overall, AFB could be cultured from 42% of the patients.

Table 3 CSF finding in different CD4 count Group

	CD4 Count Groups						f value	p value
	Group A (CD4 Count <50) (N=43)		Group B (CD4 Count 50-200) (N=34)		Group C (CD4 Count > 200) (N=23)			
	Mean	SD	Mean	SD	Mean	SD		
Protein (mg/dl)	148.3	31.64	345.6	90.14	422.6	68.40	159.623	<0.0001
Sugar (mg/dl)	27.6	6.34	28.2	5.75	28.4	6.04	0.161	0.851
ADA	39.4	15.28	38.4	15.93	35.4	18.32	0.461	0.632
Total Cells	173.5	75.57	315.6	137.48	418.1	130.44	37.968	<0.0001
Polymorph	17.4	7.48	15.0	7.28	14.2	6.42	1.8463	0.163
Lymphocytes	82.6	7.48	84.9	7.36	85.8	6.42	1.778	0.174

Outcome

Outcome of patients in the index hospitalization was also studied. 11 patients expired while 89 patients improved.

Discussions

Our results demonstrate that there are distinct differences in clinical, radiological and CSF findings between different CD4 count groups.

Most studies report similar clinical presentation of TBM in HIV infected adults as of uninfected patients.[7-13] Our study also found data similar to the historical data of previous studies with fever being the most common presentation followed by headache and nausea /vomiting. But, in our study, we found prevalence of altered sensorium in disproportionately higher percentage of patients with CD4 count less than 200 as compared to those with CD4 count more than 200. It was in 90.70% of patients in CD4 count <50, 91.18% in CD4 count 50 – 200 and only in 47.83% patients of CD4 count > 200. This could be due to the reason that patients with CD4 count < 200 present with more advanced stage of disease due to immunosuppression.

Radiological features of TBM include one or more of the following findings; hydrocephalus; basal meningeal enhancement; infarction; and tuberculoma. Normal CT/MRI and cerebral atrophy were also reported in significant number of TBM patients in the past.

In our study, normal radiological findings was found in 17% of the total TBM patients. This was similar to study done by H.K. Sharma et al.14 in their study, normal radiological findings were found in 19.5% of patients. Moreover, in that study normal findings correlated with stage of disease at presentation with most of the patients with normal finding belonged to stage 1. In our study normal radiological findings was more common in stage II as compared to stage III (32.5% Vs. 7.27%). But, none of the stage 1 patient had normal findings. This could be due to very few (only 5) stage 1 patients in our study as most of the patients which presented to us were in advanced stage.

Tuberculoma was found in 15% of the patients. Its reporting is highly variable among various studies. It was reported in 33.3% of patients by S.M. Katrak et al[12] while only in 5% of patients by Bandhyopadhyay et al.[15] Its prevalence did not varied much between groups (Group A – 11.63%, Group B – 17.65% and Group C – 17.30%).

Basal meningeal enhancement was the most common radiological finding in our patients. It was found in 47% of patients. Similar to ours it was the most common radiological findings in most other studies. It was found in only 9.3% of patients with CD4 count < 50 as opposed to 70.59% and 82.61% in CD4 count 50 – 200 and CD4 count > 200 groups. We could not find any other study which tried to study the relation between CD4 count and radiological findings. But, the most likely reason for this result is the severe degree of immunosuppression in this group which can impair the inflammatory response and hence the formation of basal exudates. Similar findings were also reported by S.M. Katrak et al.[12] They found basal meningeal enhancement in 33.3% of HIV positive patients and 81.8% of HIV negative patients (p = 0.002).They also studied the histopathological findings in some cases and found that exudates was scant in HIV positive patients. Most of the patients in their study were severely immunosuppressed though CD4 count was not done in their study.

Hydrocephalous was found in 33% of patients in this study. Similar result was found by Bandhyopadhyay et al[46] who found it in 30% of patients. Other studies have reported it in varying proportion of patients. Luma et al have reported it in 70% of patients[16] while Katrak et al in just 5.5% of patients.[29] In our study, it was distinctly less common in those with CD4 count less than 50 as compared to other groups (9.3% in CD4 count <50, 58.32% in CD4 count 50-200 and 39.13% in CD4 count > 200 group). This could again be explained by the scant exudates formation in the severely immunosuppressed patients in the former group and might be the reason behind varying results in different studies.

Hydrocephalous was found in 50.91% of patients in stage 3 as compared to just 12.5% of patients in stage 2. This is in accordance with hydrocephalous having positive association with

severe neurological deficit in TBM patients as was found by Bandhopadhyay et al.[15]

Infarct was found in 23% of all patients in our study. It was found in 13 to 50% of patients in different studies. Katrak et al found it in 38.9% of patients[12], HK Sharma et al in 14.13% of patients[14] and Bandhyopadhyay et al in 27.5% of patients. In this study, it was found in 30.91% of stage 3 patients and only 15% of stage 2 patients. Positive association of infarcts with severe neurological deficit has been seen in earlier studies.

In or study, total cell count was significantly different in the three groups (Mean $\pm$ SD is 173.5 $\pm$ 75.57, 315.6 $\pm$ 137.48 and 418.1 $\pm$ 130.44 in Group A, B and C respectively. Reduced CSF white cell count in Group A as compared to other groups may be due to severe immunsuppression and hence reduced inflammatory response in this group. Finding in the study of Thwaites et al of significantly less total cell count in HIC positive patients may be a reflection of similar phenomenon. In another study, 33% of HIV-infected TBM patients with a CD4 T-lymphocyte count less than 50 cells/ml had a normal CSF white cell count.

In our study, there was significant difference in CSF protein concentration in the three groups of CD4 counts. It was significantly less in Group A as compared to other groups (CSF protein (mg/dl) of group A is 148.3 $\pm$ 31.64, group B is 345.6 $\pm$ 90.14 and group C is 422.6 $\pm$ 68.4, p value is < 0.0001).

D. Cecchini et al also studied the CSF findings in HIV positive and negative patients.. 101 patients were HIV positive and 40 patients were HIV negative. CSF data were available for 91 HIV positive and 39 HIV negatives. CSF protein was 115 mg/dl in HIV negative group and 77 mg/dl in HIV positive patients ($p < 0.01$). They further sub-classified HIV positive patients into those with CE4 count < 50 and > 50. Median protein level was 65 (24 – 127) mg/dl and 122 (66-1999) mg/dl in the two groups.[17]

S.M. Katrak et al also studied the CSF findings of 18 HIV-P and 25 HIV-N patients. In their study, also they found protein concentration of 124 $\pm$ 88 mg/dl in HIV positive patients against a concentration of 175 $\pm$ 85 in HIV – N group. The difference was statistically significant ($p = 0.016$)[12].

In our study, 11 of the patient expired during index hospitalization, while 89 patients improved. Out of these, 7 (16.28%) patients belonged to group A, 2 patients each (5.88% and 8.7%) belonged to group B and C. This shows that mortality is more common in patients with CD4 count < 50. S.K. Bandhyopathyay et al conducted a study on 82 patients, of which 40 were HIV positive. Death occurred in 25% of HIV positive TBM patients, of which 90% were having CD4 count less than 200. On independent risk factor analysis in patients with HIV infection, a GCS score of less than 9/15, occurrence of seizure and a CD4 count of less than 200/mm^3 were strongly associated with mortality. Like earlier studies, in our study also, mortality was strongly related to the stage at presentation. All the expired patients belonged to modified BMR stage 3.[15]

Inspite of less prominent CSF and radiological findings, the mortality was visibly more in those with CD4 count less than 50. Thus, like tuberculosis of other organs (notably lung), clinical, CSF and radiological findings in HIV patients can be quite different especially in those with severe immunosuppression. Therefore, a high degree of suspicion is required when interpreting radiological and CSF findings of HIV positive TBM patient.

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