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Tubercular meningitis in HIV and non-HIV patients a comparative study from tertiary centre of central India - A prospective study

[1]Dr. Mamsi Dhakre, Resident, Department of Medicine Gajra Raja Medical College and Jay Arogya Hospital, Gwalior (M.P.)

[2]Dr. Dharmendra Tiwari, M.D. Associate Professor, Department of Medicine Gajra Raja Medical College and Jay Arogya Hospital, Gwalior (M.P.)

[3]Dr. Arvind Gupta, D.M. Assistant Professor, Department of Neurology Gajra Raja Medical College and Jay Arogya Hospital, Gwalior (M.P.)

Corresponding Author: Dr. Mamsi Dhakre, Resident, Department of Medicine Gajra Raja Medical College and Jay Arogya Hospital, Gwalior (M.P.)

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Abstract

Introduction: TB is a challenging problem and prevalent in developing countries like India, and TBM is the most frequent neurologic complication which needs to be diagnosed and treated early because of its association with high mortality and severe neurological sequelae. The data regarding the prevalence of TBM in HIV is scarce and scattered. Therefore, in this study comparison of clinical, microbiological and radiological features of TBM were done between HIV TBM and Non-HIV TBM subjects.

Methods: After the written consent 120 subjects were enrolled. Detailed history of presenting clinical symptoms, systemic examination especially neurological examination, routine blood investigation, CSF-RM, CSF CB-NAAT, HIV ELISA, CSF Culture and MRI Brain, and only confirmed patients of TBM were included into the study. On the basis of HIV status of TBM patients they are divided into two groups: TBM HIV and TBM NON-HIV. Prognosis of all admitted patients were assisted during course of hospitalization and follow up by Modified BARTHEL Index at 0, 1 and 3 months.

Results: Clinical features like fever, vomiting, headache, altered mental status, neck rigidity etc. were common in both the groups but presentation is delayed in HIV TBM subjects. On microbiological comparison CSF culture is gold standard for diagnosis of TBM but it takes more time so, CBNAAT can be used for rapid and initial diagnosis for TBM. Radiological studies depicts neurological complications like papilledema,

hydrocephalous, tuberculoma which were more common in HIV TBM than Non HIV TBM subjects.

Conclusion: HIV co-infection with TBM have an impact on the progression as well as outcome of the disease and therefore HIV testing must be done in all TBM patients.

Keywords: HIV, TBM, Tubercular meningitis.

Introduction

Tuberculous meningitis (TBM) is the most severe clinical presentation of tuberculosis and causes high mortality and morbidity, particularly in HIV-infected patients. Tubercular meningitis account for approximately 1 percentage of all cases of tuberculosis and 5-10 percentage of extrapulmonary TB cases (1). Before HIV the most important determinant for the development of TBM was age. In populations with high TB prevalence TBM differs from pulmonary, and other extrapulmonary tuberculosis, in that the peak age is from 0–4 years (2). In populations with lower TB prevalence, most cases of TBM are in adults. Risk factors identified for these people are alcoholism, diabetes mellitus, malignancy, and recent corticosteroid use. Co-infection with HIV now dwarfs these risk factors. HIV increases the lifetime risk of developing clinical TB post-infection to 1 in 3.6 HIV also predisposes to the development of extrapulmonary TB, and in particular TBM, a risk which increases as the CD4 count declines.

The disease constitutes either reactivation of latent infection, or new infection. The total number of tuberculosis cases in the world is increasing. It is estimated that most of these new cases will be in South East Asia fuel led by the rapid spread of HIV. It has been predicted that without intervention 200 million people alive today will develop TB. The physician needs to be aware of these changes, as less common forms of tuberculosis such as TBM will be encountered more often (2). Mortality from meningitis appears to be much higher in developing countries than in developed countries. Factors that contribute to this high mortality include delay in diagnosis/treatment of meningitis and severe immunosuppression in HIV-infected patients (3). Based on the clinical features alone, the diagnosis of TBM can neither be made nor excluded with certainty. Unfortunately, there is still no single diagnostic method that is both sufficiently rapid and sensitive. Most factors found to correlate with poor outcome can be directly traced to the stage of the disease at the time of diagnosis. The only way to reduce the mortality and morbidity is by early diagnosis and timely recognition of complications and institution of the appropriate treatment strategies (4). There is a high risk of co-infection of TBM and HIV due to weakened immune system resulting in delay of treatment response in co-infected subjects. Therefore, this study was aimed to compare the clinical, microbiological, radiological features and prognostic markers of tubercular meningitis in HIV infected patients (TBM HIV) and non-infected patients (TBM NON-HIV) in the Department of Medicine and Department of Neurology, G.R Medical College, Gwalior of Central India.

Materials and methods

The present study was carried out after ethical permission in the Department of Medicine and Department of Neurology in J.A. Group of Hospitals, Gwalior on an inpatient basis from January 2019 to August 2020. After the written consent 120 subjects were enrolled in this study who were confirmed cases of Tubercular meningitis (with or without HIV) and were the admitted patients of JAH Group of Hospitals. It was a hospital based prospective study.

Inclusion criteria

- Age more than 15 years.
- Cases fulfilling the criteria of Tubercular meningitis according to consensus criteria Marais et al (5) for diagnosis of Tubercular meningitis or fulfillment of essential criteria along with supportive evidence.

Exclusion criteria

- Age below 15 years.
- Cases other than tubercular causes of meningitis.
- Subjects who do not provide consent for the study.

Method of Data collection

Detailed history of presenting clinical symptoms, systemic examination especially neurological examination, routine blood investigation, CSF-RM, CSF CB-NAAT, HIV ELISA, CSF Culture and MRI Brain, in the Department of Microbiology and Department of Radiology and only confirmed patients of TBM were included into the study. On the basis of HIV status of TBM patients they are divided into two groups: TBM HIV and TBM NON-HIV. Prognosis of all admitted patients were assisted during course of hospitalization and follow up by Modified BARTHEL Index at 0, 1 and 3 months.

Statistical Analysis

The data were collected individually and then tabulated and analysed using Microsoft Excel and SPSS 16.0 version software's. Statistical Analysis was done using Pearson Chi-square test and unpaired t-test and a 'p'-value of <0.05 was considered significant. The data was analysed first for 120 TBM patients, then separated into TBM HIV and TBM NON-HIV groups to analysed the outcome on the basis of presence or absence of HIV in the TBM patients.

Observations and results

After analysing data into TBM HIV and TBM NON-HIV groups it was found that TBM was more common in males. Out of 120 TBM patients, 96 (80%) were males and 24 (20%) were female subjects with M:F ratio of 4:1.

The incidence of co-infection of TBM subjects with HIV (TBM HIV) was seen in 24.17% of the subjects and 75.83% were non-infected with HIV (TBM NON-HIV). In the TBM HIV group there were 23 (79.31%) males and 6 (20.69%) female subjects while in TBM NON-HIV group 73 (80.22%) were males and18 (19.78%) were females.

There was a non-significant (p= 0.924) difference between the mean age of TBM HIV (36.48 years) and that of TBM NON-HIV (36.78 years) subjects which indicates that the subjects of both the groups belong to same age range.

Table 1: Clinical features and Clinical Signs of the Study subjects

Features	TBM (n=120)	TBM HIV (n=29)	TBM NON-HIV (n=91)	Chi square value	Z value	P value	Significance
Fever	116 (96.67%)	29 (100%)	87 (95.6%)	1.32	1.15	0.25	Ns
Headache	73 (60.83%)	22 (75.86%)	51 (56.04%)	3.63	1.9	0.057	Ns

Vomiting	34 (28.33%)	9 (31.03%)	25 (27.47%)	0.14	0.37	0.71	Ns
Altered sensorium	75 (62.5%)	20 (68.97%)	55 (60.44%)	0.68	0.83	0.409	Ns
Seizure	39 (32.5%)	13 (44.83%)	26 (28.57%)	2.65	1.63	0.103	Ns
Papilledema	37 (30.83%)	15 (51.72%)	22 (24.18%)	7.83	2.8	0.0052	**
Stroke	7 (5.83%)	0 (0%)	7 (7.69%)	2.37	1.54	0.12	Ns
Cranial nerve palsy	38 (31.67%)	13 (44.83%)	25 (27.47%)	3.06	1.75	0.08	Ns
3rd	13 (10.83%)	4 (13.79%)	9 (9.89%)	-	-	-	-
6th	26 (21.67%)	11 (37.93%)	15 (16.48%)	-	-	-	-
5th	1 (0.83%)	0 (0%)	1 (1.099%)	-	-	-	-
7th	3 (2.5%)	0 (0%)	3 (3.297%)	-	-	-	-
Paraparesis	19 (15.83%)	7 (24.14%)	12 (13.19%)	1.98	1.41	0.159	Ns
Neck rigidity	120 (100%)	29 (100%)	91 (100%)	-	-	-	-
Kernig's sign	119 (99.17%)	29 (100%)	90 (98.9%)	0.32	0.567	0.57	Ns
Brudjinski sign	39 (32.5%)	2 (6.9%)	37 (40.66%)	11.43	3.38	0.0007	***

N= No. of subjects * Significant , ns=non-significant

As seen in Table 1, among the clinical features, the triad of the symptoms of fever, headache and vomiting was found in 28.33% of the study subjects with percentage of fever (96.67%), headache (60.83%) and vomiting (28.33%). Altered sensorium was seen in 62.5% of subjects, seizure in 32.5%, papilloedema in 30.83%, stroke in 5.83%, cranial nerve palsy in 31.67%, and paraparesis was in 15.83% subjects.

The TBM HIV subjects had similar symptoms as TBM NON-HIV although they presented in later stage of disease. Out of all the clinical symptoms the papilloedema was found significantly higher in TBM HIV subjects (51.72%) compared to TBM NON-HIV (24.18%) while remaining symptoms were non-significant statistically when compared between TBM HIV and TBM NON-HIV subjects. Cranial nerve palsy was found non-significantly (p=0.08) higher in TBM HIV subjects (44.83%) compared to TBM NON-HIV (27.47%).

Among the clinical signs (Table 1), Brudjinski sign was significantly (p=0.0007) higher in TBM NON-HIV (40.66%) group compared with TBM HIV (6.9%) group. Neck rigidity was found in 100% of the TBM subjects.

Kernig's sign was found in 100% of TBM HIV and 98.9% in TBM NON-HIV subjects which was not significant statistically.

On laboratory diagnosis, Total Leucocyte Count (TLC) of blood in our study subjects was very significantly higher with mean value of 8252 cells/cumm of blood in TBM NON-HIV than 4891 cells/cumm in TBM HIV subjects. The mean value of CD4 count of HIV subjects was 419 in TBM HIV subjects. CSF CBNAAT was significantly positive in 96.55% of TBM HIV subjects and 48.35% of TBM NON-HIV subjects while CSF CULTURE positivity was seen in zero percent of TBM cases.

On Routine and Microscopic findings of CSF (Table 2) of study subjects, the CSF findings of cells and proteins were significantly higher in TBM HIV subjects but CSF glucose was non-significantly higher in TBM NON-HIV subjects.

Table 2: Routine and Microscopic findings of CSF of study groups

Unpaired t test	CSF CELLS (cells/mm3)		CSF PROTEIN (mg/dl)		CSF GLUCOSE (mg/dl)	
	TBM HIV	TBM NON-HIV	TBM HIV	TBM NON-HIV	TBM HIV	TBM NON-HIV
N	29	91	29	91	29	91
Mean	205.7	142.6	749.9	231.2	39.86	41.01
Std. Deviation	151	146	606	199	13.1	14.8
Std. Error of Mean	28.04	15.29	112.5	20.86	2.44	1.56
P value	0.0468		<0.0001		0.7093	
P value summary	*		****		Ns	
Significantly different (P < 0.05)?	Yes		Yes		No	
t value	t=2.009		t=7.103		t=0.3737	
Difference between means	-63.01 ± 31.36		-518.8 ± 73.04		1.152 ± 3.083	
95% confidence interval	-125.1 to -0.9056		-663.4 to -374.1		-4.953 to 7.257	

N= No. of subjects * Significant ,ns=non-significant

Chest X-Ray findings suggestive of active (cavitatory) lesion in 21.67% of TBM cases which was indicative of the extra neural tubercular manifestations in TBM subjects. Also the active lesions was found very significantly higher in TBM HIV (51.72%) than TBM NON-HIV (12.09%) subjects while the old (calcified) lesions was significantly (p=0.03) higher in TBM NON-HIV (14.29%) subjects and zero% in TBM HIV subjects.

Neuroimaging (CT/MRI) findings of the study subjects (Table 3) reveals the hydrocephalus (30 %) as the most common finding. The feature of basal exudates was found very significantly (p<0.0001) higher in TBM HIV subjects (48.28%) compared to TBM NON-HIV (13.19%). Hydrocephalus (44.83% and 25.27%) and tuberculoma (27.59% and 9.89%) were found

significantly ($p<0.05$) higher in TBM HIV and TBM NON-HIV groups respectively. Contrast enhancement and infarct were non-significantly higher in TBM HIV subjects.

Table 3: Neuroimaging (CT/MRI) findings of the study subjects

CT/MRI Features	TBM	TBM HIV	TBM NON-HIV	Chi square value	Z value	P value	Significance
Hydrocephalus	36 (30%)	13 (44.83%)	23 (25.27%)	4.0	2.0	0.045	*
Basal exudates	26 (21.67%)	14 (48.28%)	12 (13.19%)	15.95	3.99	<0.0001	****
Contrast enhancement	26 (21.67%)	10 (34.48%)	16 (17.58%)	3.7	1.9	0.054	Ns
Tuberculoma	17 (14.17%)	08 (27.59%)	09 (9.89%)	5.7	2.4	0.017	*
Infarct	33 (27.5%)	10 (34.48%)	23 (25.27%)	0.94	0.97	0.33	Ns

* Significant ns=non-significant

Discussion

In this study, out of the 120 registered TBM patients, 96 (80%) were males and 24 (20%) were female subjects i.e. TBM was found more common in males. Similar to our study Kaur et al(6) also found TBM to be more common in males.

The incidence of co-infection of TBM with HIV (TBM HIV) was seen in 24.17% of the subjects and remaining 75.83% were non-infected with HIV (TBM NON-HIV). In Por Mohammad et al (7) study co-infection was seen in 38% of the subjects. In a study by Kaur et al (6) at Northern region of India on adult TBM patients 7.27% of the subjects were found co-infected with HIV which was very less compared to our study while in Mouna et al (8) study 92% co-infection was noticed, which may be due to regional and environmental variation.

In this study there was a non-significant difference between the mean age of TBM HIV (36.48 years) and that of TBM NON-HIV (36.78 years) subjects. Similar to our study the mean age of TBM subjects were 36.42 years in Kaur et al (6) study. Nearly similar age was seen in Thwaites et al (9) study with the median age of 34 years in cases (10). In Seth et al (11) study, the median age of cases was 22 years (11) which was comparatively indicating the younger age than rest of the studies.

The TBM HIV subjects had similar symptoms as TBM NON-HIV although they presented in later stage of disease and had higher frequency of extra-neural presentation as reported by Thwaites et al (9). Katrak et al (12) also found no difference in the clinical features of both the groups but cognitive dysfunction was more common amongst HIV positive group.

It is difficult to differentiate the clinical picture of TBM from various other types of meningitis. According to some authors the illness of more than 5-6 days of is a predictor of TBM (10,13). In this study the triad of the symptoms of fever, headache and vomiting was found in 28.33% of the study subjects with percentage of fever (96.67%), headache (60.83%) and vomiting (28.33%). In

Kaur et al (6) study, these triad of symptoms was found in 60% of the cases with illness history for at least 14 days including percentage of fever (90.9%), headache (72.7%) and vomiting (54.5%). This may be due to strict inclusion criteria of fever, headache and vomiting in our and Kaur et al (6) studies. The percentage of these symptoms were nearly similar or higher in some studies (4,13,14). The triad symptoms along with neck stiffness was seen common by Pehlivanoglu et al (15) study in Turkey. In Luma et al (3) study 74.1% of HIV-TBM patients had headache as their main symptom. In Croda et al (1) study 15% had fever, headache, and meningeal signs simultaneously. Some studies suggested the delay in presentation or the absence of headache as a predictor of mortality in TBM cases (16,17).

In this study altered sensorium was seen in 62.5% of subjects, seizure in 32.5%, papilloedema in 30.83%, stroke in 5.83%, cranial nerve palsy in 31.67%, and paraparesis was in 15.83% subjects. Out of all the clinical symptoms the papilloedema was found significantly higher in TBM HIV subjects (51.72%) compared to TBM NON-HIV (24.18%) while remaining symptoms were non-significant statistically when compared between TBM HIV and TBM NON-HIV subjects. In Kaur et al (6) study seizure was found slightly higher than other symptoms while in our study other than the triad of symptoms altered sensorium was seen higher than other symptoms. In our study 6th cranial nerve was most commonly involved in TBM (21.67%) subjects while 9% in Kaur et al (6) study which is consistent with other studies as well.

In our study Kernig's sign was found in 100% of TBM HIV and 98.9% in TBM NON-HIV subjects. Neck rigidity was seen in 100% subjects of our study while it was found in 67.3% in Kaur et al (6) study. In some studies neck rigidity seen to be ranged from 18% to 91% (10,13).

In our study CSF CBNAAT was significantly positive in 96.55% of TBM HIV and 48.35% of TBM NON-HIV subjects whereas CSF culture positivity was seen in zero percent of TBM cases. In Pehlivanoglu et al (15) study the culture positivity was high and seen in 39.9% of patients.

The CSF findings of TBM patients were been described by many review articles (7,18) as having pleocytosis of more than 20 cells/mm3, proteins more than 100mg/dl and CSF sugar less than 60% of corresponding blood sugar. Our study results were corresponds with the results of the review articles with the mean value of 158 cells/mm3, 357 mg/dl proteins and 40.7mg/dl CSF sugar. The CSF findings of this study were significantly higher in TBM HIV subjects which were also consistent with the usual observation of CSF picture suggestive of TBM as seen by various authors (6,13). In Christensen et al (13) study at Denmark, 86% had elevated CSF protein, 90% had elevated WBC count and 50% patients had CSF: blood glucose ratio of less than 0.33. Torok et al (19) findings of CSF shown neutrophils predominance in 63%, smear positive in 69% and culture positive in 87.9%.

In our study active lesion in CXR was seen in 21.67% of TBM cases which was indicative of the extra neural tubercular manifestations in TBM subjects. Also the active lesions was found very significantly higher in TBM HIV (51.72%) than TBM NON-HIV (12.09%) subjects. In our and Kaur et al (6) studies the extra neural TB manifestations were less as compared with some other studies (10,13). In Karstaedt et al (20) study HIV-infected 18-59 year age group had significantly

more extra neural TB compared to the non-HIV-infected (76.9% vs. 9.1%)

The neuroimaging (CT/MRI) findings of this study reveals the hydrocephalus (30 %) as the most common finding in TBM subjects. Similar to our study many other studies had hydrocephalus as the most common finding in the study subjects. In Kaur et al (6) study hydrocephalus was found in 24%, 29% in Christensen et al (13) study and 70.6% in Luma et al (3) study. Higher frequency of hydrocephalus at tertiary care centre may be due to the referral bias, as mentioned earlier (6).

The next common neuroimaging findings (Table 3) in our study for TBM subjects were infarct (27.5 %) > basal exudates (21.67%) = contrast enhancement (21.67%) > tuberculoma (14.17%). In Kaur et al (6) study basal exudates (22%) > meningeal enhancement (20%) > tuberculomas (7%) and infarcts (3.6%) while in Christensen et al (13) study infarcts (29%) > tuberculomas (14%). In Pehlivanoglu et al (15) study tuberculomas and basal meningitis were most common neuroimaging findings.

In our study the total mortality of TBM subjects were 41.67% (10% at 1 month follow up while it increases to 31.67% at 3 month follow up) which was very high and might be due to registration of most of the patients in the later stages of TBM. In TBM HIV subjects the total mortality was seen in 51.72% subjects which was higher than TBM NON-HIV subjects (38.46%). Nearly similar mortality seen in Kaur et al (6) study with total mortality of 43.63% in TBM patients where all the HIV positive cases died showing high rates of mortality in TBM HIV co-infection. In Christensen et al (13) study in Denmark the mortality rate was 19% which was very lower than other studies including ours. 69% of mortality was seen in Karstaedt et al (20) study in South Africa while 63.3% in Cecchini et al (21) study and 67.2% in Torok et al (19) study in Vietnam which was due to the endemicity of TB in these areas.

In our study the prognosis of TBM subjects were correlated with male gender, fever, altered sensorium, neck rigidity, Kernig's sign as clinical features; hydrocephalus and infarct in neuroimaging; active TB; and high CSF cells and proteins. When compared between TBM HIV and TBM NON-HIV groups male gender, papilledema, Brudjinski sign, CSF CBNAAT, CSF cells and proteins, basal exudates> hydrocephalus >tuberculoma and active>old TB were the predictors of mortality.

In many other studies (17,19) delayed treatment, female gender, infarction, low CSF glucose levels, low CSF: blood glucose ratio and high CSF protein concentration were the observed factors to predict mortality in TBM cases while Kaur et al (6) study did not reveal any such association with these variables.

In Kaur et al (6) study the predictors of mortality were age ≥ 40 years, loss of appetite, loss of weight, evidence of extra neural TB, past history of TB and presence of basal exudates and hydrocephalus. In George et al (16) study, age > 40 y, Glasgow coma scale score <8, CSF protein ≤60 mg% and MRC stage III were found to be the predictors of mortality in TBM. In Sheu et al (17) study in Taiwan also observed age >60 years was associated with high mortality. Similar to our finding Girgis et al (22) also found hydrocephalus as a risk factor for high mortality in TBM.

Overall it was found that clinical features like fever, vomiting, headache, altered mental status, neck rigidity etc. were common in both the groups but presentation is delayed in HIV TBM subjects. Radiological studies depicts neurological complications like papilledema,

hydrocephalous, tuberculoma were more common in HIV TBM than Non HIV TBM subjects.

On microbiological comparison CBNAAT was found to be effective and sensitive in the diagnosis of TBM. CSF culture is gold standard for diagnosis of TBM but it takes more time so, CBNAAT can be used for rapid and initial diagnosis for TBM. To summarise mortality and morbidity were high in HIV TBM than non-HIV TBM subjects. In spite of treatment the prognosis was found to be poor in HIV TBM subjects. So it was concluded that HIV co-infection with TBM have an impact on the progression as well as outcome of the disease and therefore HIV testing must be done in all TBM patients.

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