Original Article

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Clinical Profile and Treatment Response in Tuberculous Meningitis- A Comparison between HIV Positive and HIV Negative Patients

Internal Medicine Section

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ABSTRACT

Introduction: Tuberculous Meningitis (TBM) is a common infection in patients with Human Immunodeficiency Virus (HIV) and it shows significant differences in clinical profile, treatment response, and outcome compared to patients without HIV infection.

Aim: To describe the clinical presentation, laboratory parameters, and radiological findings of TBM patients with and without HIV co-infection and to observe differences between them in treatment response, complications, and mortality.

Materials and Methods: This was a prospective observational study, conducted on 80 TBM patients with (n=40) and without (n=40) HIV co-infection at Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India, from from March 2016 to August 2017. Demographic, clinical, laboratory data, and various imaging findings were noted at the start of the study and at three and six months follow-up, for any changes from baseline to know the treatment response. Appropriate statistical tests were applied, and p-value less than 0.05 were considered statistically significant.

Results: Mean age of HIV patients was 36.75 years and that of the non HIV patients was 29.35 years. Altered sensorium (90% in HIV and 72.5% in non HIV), seizures (50% in HIV and 20% in non HIV) were common in HIV patients, and weight loss (95% in non HIV and 87.5% in HIV) was common in non HIV patients. Common signs noted were nuchal rigidity (90% in HIV and 87.5% in the non HIV group), focal neurological deficit (50% in HIV and 22.5% in non HIV), and cranial nerve palsy (37.5% in HIV and 12.5% in non HIV). Anaemia was seen in 56.3% (87.5% in HIV and 25% in non HIV) and raised Erythrocyte Sedimentation Rate (ESR) was seen in 56.3% (25% in HIV and 87.5% in non HIV) patients. Tuberculoma was the most common (32.5%) Magnetic Resonance Imaging (MRI) brain finding. Adverse drugs reactions due to Antitubercular Treatment (ATT) (other causes ruled out) were seen in 22.5% of HIV patients (none in non HIV), and Antiretroviral Therapy (ART)-induced Adverse Drugs Effects (ADE) was noted in 10% of patients. Patient survival was better among non HIV (65%) compared to HIV (55%) patients. Multidrug-resistant Tuberculosis (MDR-TB) was more prevalent in HIV (7.5%) than non HIV (2.5%) cases.

Conclusion: TBM involves a younger population, has a worse prognosis in HIV co-infection patients with more adverse reactions to treatment.

Keywords: Antiretroviral therapy, Antituberculous therapy, Human immunodeficiency virus, Tuberculosis

INTRODUCTION

India's contribution of 1.8 million TB cases in 2020 was the highest (26% of the global cases) in the whole world as per the World Health Organisation (WHO) Global TB report 2021. Also, 38% of global TB death in HIV negative and 34% of combined (HIV positive and HIV negative) TB deaths were contributed by India in 2020. The risk of developing TB is estimated to be between 15-21 times greater in people living with HIV than those without HIV infection [1]. Globally, 37.7 million people were living with HIV in 2020 with 1.5 million new cases and about 0.68 million dying from HIV-related causes [2].

Tuberculosis is the most common opportunistic infection in HIV infected persons [3]. Cases of TBM are commonly seen in HIV patients even though the exact incidence and prevalence have been not known. Many observational studies have shown no major difference in clinical features, laboratory investigations, radiological findings, treatment response in TB patients with and without HIV [4,5].

Literature is replete with studies that highlight the difference between the clinical presentations of HIV-TB co-infection with those of non HIV TBM. Clinically, TBM with HIV co-infection presents with more altered sensorium and impaired cognition compared to non HIV patients [6,7]. Laboratory parameters of HIV-TBM in various studies have shown Cerebrospinal Fluid (CSF) features like low CSF cell count, low protein and high CSF mycobacterial culture yield and haematological features of anaemia and hyponatremia [6-9]. They also have evidence of extrameningeal disease with more meningeal enhancement and cerebral infarcts on brain imaging compared to non HIV TBM patients [5-7,10]. Response to treatment is poor in HIV-TBM patients due to high incidence Multidrug-Resistant Tuberculosis (MDR-TB) and ART drug interactions as well as they have poor outcome with high mortality as shown by various studies [5-10].

As per WHO and National AIDS Control Organisation (NACO) guidelines, all HIV infected TB patients should be started on ART with whatever CD4 counts they have, usually after two weeks of starting AKT and before two months (eight weeks); except for those with CD4 less than 50/cmm where ART should be started within two weeks. In TBM patients with HIV co-infection, caution is needed since immediate ART (2-8 weeks) can lead to more severe adverse events like immune reconstitution inflammatory syndrome instead of initiating ART two months after the start of TB treatment [11,12]. Patients with HIV-TB co-infection have a very high incidence of multidrug resistant TB along with increased mortality rate [13,14]. As major differences in clinical, laboratory and radiological features are noted in TBM patients co-infected with HIV along with high mortality and MDR-TB rates compared to non HIV TBM, it becomes essential to study them. It was an unmet need to conduct this study at this tertiary care centre to identify and compare various clinical presentations, laboratory investigations, radiographic features, and outcomes among TBM cases in patients with and without HIV co-infection.

MATERIALS AND METHODS

This was a prospective observational study conducted on 80 TBM patients (40 with HIV co-infection and 40 without HIV) at Lokmanya

Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India; over 18 months from March 2016 to August 2017. Approval of Institutional Ethics Committee (IEC) was taken for the study {letter number: SRS/184/16 (Reference ID: D0201681) dated 30/03/2016}.

Inclusion criteria: All HIV positive and HIV negative patients, >12 years of age with history of fever for five days or more, with features suggestive of meningitis (headache, neck pain and neck stiffness with weight loss or poor weight gain, night sweats) or with features suggestive of encephalitis (altered sensorium, focal deficits, seizures) with or without the involvement of cranial nerves and pyramidal tracts or combination of both. Patients with CSF findings or cerebral imaging findings {Computed Tomography (CT)/MRI finding suggestive of hydrocephalus/basal meningeal enhancement/infarct/tuberculoma} fulfilling Marais criteria for TBM were included [15].

Exclusion criteria: All HIV positive and HIV negative patients already on antitubercular therapy for TB elsewhere were excluded from the study.

Sample size calculation: The incidence of TB patients was approximately 800-1200 patients/year at the study centre with around 10% incidence of TBM (approximately 80-120 patients) among them. Considering this, the sample size of 80 was determined and patients were selected by consecutive random sampling methods.

Study Procedure

Demographic data, the relevant clinical history (including >10% weight loss over six months) and examination, laboratory investigations including detailed CSF analysis, radiological imaging findings, and response to treatment including adverse drug reactions were documented in case sheets.

Scores were given based on clinical features, CSF, imaging findings, and extra-neural TB as per Marai's Criteria and patients diagnosis was classified as definite TBM {demonstration of TB bacilli on smear, positive culture or Cartridge Based Nucleic Acid Amplification Test (CBNAAT) or histological evidence}, probable TBM (total score >12) and possible TBM (total score between 9-11) [15].

Follow-up of the patients was done at three months and at six months intervals for documenting changes in clinical profile and response to treatment. Routine investigations were done in all patients at three months and six months intervals, and CD4 count was done at six months. MRI brain was repeated for all patients at three months or earlier if needed (if clinical deterioration).

The Adverse Drug Effects (ADE) of ATT and ART were documented based on clinical assessment and routine laboratory investigations. Relevant changes in treatment were made by the treating physician if drug induced side-effects were noted, as per existing Revised National TB Control Programme (RNTCP) and National AIDS Control Organisation (NACO) guidelines [12].

All the above mentioned data were studied and compared between HIV positive and HIV negative groups. During follow-up, worsening of clinical features due to the development of hydrocephalus, vasculitis, new infarcts, and Immune Reconstitution Inflammatory Syndrome (IRIS) were noted. Paradoxical response to antitubercular therapy was treated with a short course of oral prednisolone (0.5 mg/kg) for two weeks and was gradually tapered off.

STATISTICAL ANALYSIS

The data was entered in Microsoft excel 2010 spreadsheet and was analysed using Statistical Package for Social Sciences (SPSS) version 2010. Qualitative variables were represented in the form of frequency tables and percentages, bar diagrams, pie charts, and quantitative data as mean and standard deviation. Association between two qualitative data was calculated using Chi-square test/Fisher's-exact test and comparison of the mean of quantitative data between two groups was made using unpaired t-test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, 80 patients of TBM were enrolled, 40 were HIV positive and 40 were HIV negative. The mean age of patients were 36.75 years (range 15-55 years) in HIV positive and 29.35 years (range 14-65 years) in HIV negative patients, suggesting the involvement of the younger population among non HIV patients. There was equal (M:F 1:1) gender distribution among HIV patients, whereas females (70%) were more affected than males (30%) among non HIV patients [Table/Fig-1].

Gender		HIV status		Total	p-value (Chi-square)
		Positive	Negative		
Female	n (%)	20 (50.0%)	28 (70.0%)	48 (60.0%)	0.068 (3.333)
Male	n (%)	20 (50.0%)	12 (30.0%)	32 (40.0%)	
Total	N (%)	40 (100.0%)	40 (100.0%)	80 (100.0%)	

[Table/Fig-1]: Gender distribution of patients.

The most common symptom observed in HIV positive TBM patients was altered sensorium (90%) and in HIV negative patients it was weight loss (95%) besides common symptoms of meningitis (vomiting, headache and fever) observed in both the groups [Table/Fig-2]. The most common sign observed in both groups was nuchal rigidity (88.8%), focal neurological deficit (36.3%), and Cranial nerve palsy (22.5%) which were commonly seen in HIV positive patients [Table/Fig-3]. The most common cranial nerve involved were 6th cranial nerve followed by 3rd and 7th.

Symptoms	HIV status		Total n (%)	p-value
	Positive n (%)	Negative n (%)		
Fever >5 days	39 (97.5%)	39 (97.5%)	78 (97.5%)	1.000
Weight loss	35 (87.5%)	38 (95.0%)	73 (91.2%)	0.432
Cough >2 weeks	4 (10.0%)	4 (10.0%)	8 (10.0%)	1.000
Vomiting	40 (100.0%)	40 (100.0%)	80 (100.0%)	-
Headache	40 (100.0%)	40 (100.0%)	80 (100.0%)	-
Blurring of vision	8 (20.0%)	9 (22.5%)	17 (21.3%)	0.785
Altered sensorium	36 (90.0%)	29 (72.5%)	65 (81.3%)	0.045
Seizure	20 (50.0%)	8 (20.0%)	28 (35.0%)	0.004

[Table/Fig-2]: Comparison of symptoms of TBM.
Chi-square test was used for p-value; p-value <0.05 considered significant

Signs	HIV status		Total n (%)	p-value
	Positive n (%)	Negative n (%)		
Nuchal rigidity	36 (90.0%)	35 (87.5%)	71 (88.8%)	0.723
Cranial nerve palsy	15 (37.5%)	3 (12.5%)	18 (22.5%)	0.001
Focal neurological deficit	20 (50.0%)	9 (22.5%)	29 (36.3%)	0.010

[Table/Fig-3]: Comparison of clinical signs.
Chi-square test was used for p-value; p-value <0.05 considered significant

Majority (87.5%) of HIV positive patients were anaemic (Hb 11.2±1.39) as compared to HIV negative patients (25%, Hb 11.06±1.64) on presentation [Table/Fig-4,5]. Out of 40 HIV positive TBM patients, 13 (32.5%) were started on ART after AKT initiation and 27 (67.5%) were already on ART before the start of the ATT regimen. Patients of HIV were on following ART regimen-Tenofovir+Lamvudine+Efavirenz (80%), Zidovudine+Lamvudine+Nevirapine (15%) and Zidovudine+Lamvudine+Efavirenz (5%). Liver enzymes {Serum Glutamic Oxaloacetic Transaminase (SGOT)} were raised in 20 (50%) HIV positive patients after starting treatment, out of which four were on ATT and 16 patients were on both. In non HIV TBM patients, SGOT was raised in 11 (27.5%) patients after starting on AKT. Raised Serum Glutamic Pyruvic Transaminase (SGPT) was found

in 9 (22.5%) patients in HIV positive patients (1 was on ATT and 8 on both ART and ATT) and 2 (5%) patients in HIV negative group (p-value=0.023). All cases of suspected ART-induced hepatitis were asymptomatic and resolved without therapy modification. High creatinine was seen in 4 (10%) TBM patients with HIV (2 were on ATT and 2 on combined ATT and ART) and 2 (5%) patients with non HIV TBM (p-value=0.396) after starting treatment. This difference may be due to multiple risk factors causing AKI in HIV positive patients like HIV Associated Nephropathy (HIVAN), antiretroviral (Tenofovir), and anti-TB treatment (Rifampicin). Hyponatremia was found in 16 (40%) patients of HIV and 15 (37.5%) patients without HIV (p-value 0.818). Another statistically significant laboratory abnormality observed was high ESR in HIV negative group (87.5%) compared to HIV positive group (25%), probably due to a better immune response in the former group [Table/Fig-4].

Laboratory investigations		HIV status		Total n (%)	p-value (Chi-square)
		Positive n (%)	Negative n (%)		
Hb (g/dL) (M<13, F<12)		35 (87.5%)	10 (25.0%)	45 (56.3%)	0.0001 (31.75)
Total bilirubin (mg/dL)	>1.2	1 (2.5%)	2 (5.0%)	3 (3.8%)	0.556 (0.346)
Raised SGOT (IU/L)	>40	20 (50.0%)	11 (27.5%)	31 (38.8%)	0.039 (4.266)
Raised SGPT (IU/L)	>56	9 (22.5%)	2 (5.0%)	11 (13.8%)	0.023 (5.165)
Serum creatinine (mg/dL)	>1.2	4 (10.0%)	2 (5.0%)	6 (7.5%)	0.396 (0.721)
Sodium (mEq/L)	<135	16 (40.0%)	15 (37.5%)	31(38.8%)	0.818 (0.053)
ESR (mm/hr) (M>15, F>20)		10 (25.0%)	35 (87.5%)	45 (56.3%)	0.0001 (31.75)

[Table/Fig-4]: Laboratory findings.
p-value <0.05 considered significant

Laboratory investigations	HIV status			
	HIV Positive		HIV Negative	
	Mean (SD)	Range	Mean (SD)	Range
Haemoglobin	11.2 (1.39)	7-13.9	11.06 (1.64)	7-15.2
Total bilirubin	0.72 (0.20)	0.4-1.8	0.67 (0.18)	0.5-1.4
SGOT	61.9 (69.57)	13-400	36 (15.36)	13-98
SGPT	45.35 (53.28)	9-345	30.02 (18.37)	9-112
BUN	11.6 (3.86)	6-29	11.62 (3.92)	5-24
Serum creatinine	0.81 (0.21)	0.2-1.3	0.71 (0.21)	0.1-1.3
Sodium	135.2 (5.42)	116-144	136.6 (4.37)	127-144
ESR	69.6 (22.90)	20-120	61.8 (24.48)	9-108

[Table/Fig-5]: Laboratory parameters during admission.

Most common abnormality in CT brain of TBM cases on admission was tuberculoma (22.5% in HIV positive and 35% in non HIV) [Table/Fig-6]. MRI Brain on admission showed tuberculoma in 32.5% (both groups), meningeal enhancement in 17.5% (12.5% in HIV and 22.5% in non HIV), vascular infarct in 17.5% (12.5% in HIV and 22.5% in non HIV), basal exudates in 17.5% (both group) and hydrocephalus in 15% (both groups).

CT scan on admission	HIV status		Total n (%)	p-value (Chi-square)
	Positive n (%)	Negative n (%)		
Tuberculoma	9 (22.5%)	14 (35.0%)	23 (28.8%)	0.216 (1.526)
Vascular infarct	5 (12.5%)	3 (7.5%)	8 (10.0%)	0.456 (0.556)
Hydrocephalus	5 (12.5%)	3 (7.5%)	8 (10.0%)	0.456 (0.556)
Basal meningeal enhancement	4 (10.0%)	10 (25.0%)	14 (17.5%)	0.077 (3.117)
Basal exudates	8 (20.0%)	4 (10.0%)	12 (15.0%)	0.21 (1.569)

[Table/Fig-6]: Comparison of various findings on CT brain imaging.

On CSF analysis, total cell count was in the range of 5-500 cells/cmm (80% in HIV and 87.5% in Non HIV) along with lymphocyte predominance (>50%) was present in 83.8% of cases favouring a diagnosis of TBM. CSF proteins levels were raised (≤1000 mg/dL) in 88.8% of cases; CSF glucose to plasma glucose ratio of less than 50% in 75% of cases and high adenosine deaminase (>5 IU/L) level in 87.5% (80% in HIV positive and 95% in HIV negative) especially in HIV negative patients were observed [Table/Fig-7].

Parameters		HIV status		Total n (%)
		Positive n (%)	Negative n (%)	
CSF appearance	Clear	35 (87.5%)	37 (92.5%)	72 (90.0%)
	Haemorrhagic	1 (2.5%)	1 (2.5%)	2 (2.5%)
	Hazy	1 (2.5%)	0 (0%)	1 (1.3%)
	Xanthochromic	1 (2.5%)	1 (2.5%)	2 (2.5%)
	Not done	2 (5.0%)	1 (2.5%)	3 (3.8%)
Cells (cells/mm^3)	<5	1 (2.5%)	0 (0.0%)	1 (1.3%)
	5-500	32 (80.0%)	35 (87.5%)	67 (83.8%)
	>500	5 (12.5%)	4 (10.0%)	9 (11.3%)
Lymphocytes %	≤50	6 (15.0%)	4 (10.0%)	10 (12.5%)
	>50	32 (80.0%)	35 (87.5%)	67 (83.8%)
CSF protein (mg/dL)	≤1000	34 (85.0%)	37 (92.5%)	71 (88.8%)
	>1000	4 (10.0%)	2 (5.0%)	6 (7.5%)
CSF glucose (mg/dL)	≤50	30 (75.0%)	30 (75.0%)	60 (75.0%)
	>50	8 (20.0%)	9 (22.5%)	17 (21.3%)
CSF ADA (U/L)	0-5	6 (15.0%)	1 (2.5%)	7 (8.8%)
	>5	32 (80.0%)	38 (95.0%)	70 (87.5%)

[Table/Fig-7]: Comparison of CSF findings.

Among 80 TBM patients, 22 (55%) survived in HIV co-infection and 26 (65%) survived in non HIV with maximum mortality within the initial 6 months of diagnosis [Table/Fig-8]. TBM with its complications (vasculitic infarct with hemiparesis, raised intracranial tension due to obstructive hydrocephalus) and tuberculoma was the most common cause of death in HIV positive (94.4%) as well as in HIV negative patients (64.2%). Other contributing causes of death included widespread disseminated TB (cervical lymphadenopathy, military spread, abdominal and spinal TB) as well as different co-morbid conditions.

Final outcome	HIV status		Total n (%)	p-value (Chi-square test)
	Positive n (%)	Negative n (%)		
Death	18 (45.0%)	14 (35.0%)	32 (40.0%)	0.361 (0.833)
Survived	22 (55.0%)	26 (65.0%)	48 (60.0%)	

[Table/Fig-8]: Association between final outcome in both the groups.

All symptoms/signs improved at 6 months follow-up in both groups except for 1 HIV positive patient who had a focal neurological deficit which was static [Table/Fig-9]. At 3 month follow-up with MRI brain imaging, lesion improved in 14 (35%) patients in HIV positive patients and 18 (45%) HIV negative patients; whereas in 3 HIV positive cases it remained static and 2 HIV positive cases it worsened.

During follow-up 3 (7.5%) patients in HIV positive group and 1 (2.5%) patient in HIV negative group were found Multidrug-resistant TB proven on Cartridge-Based Nucleic Acid Amplification Test (GeneXpert or CB-NAAT) [Table/Fig-10].

As per Marais criteria, 28 (70%) patients in HIV positive group and 25(62.5%) patients in HIV negative group were diagnosed as probable TBM whereas 12(30%) patients in HIV positive group and 15(37.5%) patients in HIV negative group were diagnosed as possible TBM [Table/Fig-11].

Incidence of ADE due to ATT was noted in 22.5% of HIV positive patients and none in HIV negative at 6 month follow-up [Table/Fig-12]; whereas ADE due to ART was seen in 10% of patients of HIV positive group at 6 month follow-up [Table/Fig-13].

Presence of symptoms/Signs	On admission N (%)		At 3 months follow-up N (%)		At 6 months follow-up N (%)	
	HIV Positive	HIV Negative	HIV Positive	HIV Negative	HIV Positive	HIV Negative
Fever	39 (97.5%)	39 (97.5%)	5 (12.5%)	5 (12.5%)	0	0
Headache	40 (100%)	40 (100%)	15 (37.5%)	11 (27.5%)	0	1 (2.5%)
Altered sensorium	36 (90.0%)	35 (87.5%)	5 (12.5%)	0	0	0
Cranial nerve palsy	15 (37.5%)	3 (12.5%)	2 (5%)	0	0	0
Focal neurological deficit	20 (50.0%)	9 (22.5%)	5 (12.5%)	7 (17.5%)	1 (2.5%)	0

[Table/Fig-9]: Comparison of presence of clinical symptoms/signs at various time interval in both the groups (n=80).

MDR (Genexpert proven)		HIV status		Total	p-value (Chi-square test)
		Positive	Negative		
Yes	n (%)	3 (7.5%)	1 (2.5%)	4 (5.0%)	0.305 (1.053)
No	n (%)	37 (92.5%)	39 (97.5%)	76 (95.0%)	
Total	N (%)	40 (100.0%)	40 (100.0%)	80 (100.0%)	

[Table/Fig-10]: Percentage of MDR Koch (Genexpert Proven) in both the groups (n=80).

Final diagnosis		HIV status		Total	p-value (Chi-square test)
		Positive	Negative		
Possible TBM	n (%)	12 (30.0%)	15 (37.5%)	27 (33.8%)	0.478 (0.503)
Probable TBM	n (%)	28 (70.0%)	25 (62.5%)	53 (66.3%)	
Total	N (%)	40 (100.0%)	40 (100.0%)	80 (100.0%)	

[Table/Fig-11]: Percentage and association between final diagnosis in both the groups (n=80).

Adverse effect at 6 months of AKT	HIV status		Total n (%)	p-value (Chi-square test)
	Positive n (%)	Negative n (%)		
Absent n (%)	31 (77.5%)	40 (100%)	71 (88.8%)	0.001 (10.141)
Present n (%)				
Hepatitis	4 (44.4%)	0	9 (11.3%)	
Acute kidney inury	2 (22.2%)			
Hypothyroidism	1 (11.1%)			
Hyperuricaemia	1 (11.1%)			
Flu like syndrome	1 (11.1%)			
Total	40 (100.0%)	40 (100.0%)	80 (100.0%)	

[Table/Fig-12]: Comparison of adverse effect of AKT between the groups (n=80). p-value <0.05 considered significant

Adverse effect at 6 month of ART	HIV status Positive n (%)	p-value (Chi-square test)
Absent n (%)	36 (90%)	0.166 (1.920)
Present n (%)		
Hepatitis	3 (75%)	
Acute kidney injury	1 (25%)	
Total	40 (100%)	

[Table/Fig-13]: Adverse effects of ART at 6 month follow-up.

Common adverse effects of ART noted in the study were rash (Efavirenz), headache, hepatitis (Efavirenz), nephritis (Tenofovir), nausea, giddiness, hyperlipidaemia, anaemia/pancytopenia (Zidovudine). In HIV patients common side-effects of ATT noted were hepatitis, AKI, and hypothyroidism, whereas in HIV negative patients it were hepatitis, hyperuricaemia, and flu-like syndrome. AKT was modified in cases of hepatitis (diagnosed after ruling out viral and other causes) to ethambutol, streptomycin, and fluoroquinolones till hepatitis resolved, and then sequentially AKT was started to find out the culprit drug which was excluded from the regimen. In the case of AKT-induced AKI, the regimen was modification as giving isoniazid, rifampicin daily (full dose), and pyrazinamide, and ethambutol (50% of dose) on an alternate day till AKI resolved.

DISCUSSION

The TBM is one of the most severe clinical presentations of TB with very high mortality and morbidity, especially in immune-compromised patients. Despite advancements in diagnostic technologies, early diagnosis of TBM continues to be difficult. The usual practice for initiation of empirical treatment for TBM is still based on clinical features and CSF analysis findings. There is limited data of large series from developing countries regarding confirmed TBM [16].

In this study, there were enrolled 80 patients of TBM with and without HIV co-infection with 40 patients in each group. The purpose was to study the differences between the two groups in various clinical presentations, laboratory investigations, brain imaging findings, CSF analysis, course of the disease, and response to treatment during follow-up in various parameters. Our study has shown that the younger population is affected in both groups, especially in HIV negative patients. Similar findings were observed by Pehlivanoglu F et al., in Turkey where young adults aged 15-30 years have the highest incidence of TBM [16].

Clinical features showed that HIV positive patients had severe neurological manifestations like altered sensorium (p-value 0.045) and seizures (p-value=0.004). Similarly, cranial nerve palsy (p-value=0.001) and focal neurological deficit (p-value=0.01) were commonly seen in HIV positive patients. Marais S et al., conducted a retrospective study on 106 HIV-TBM co-infection patients and have shown that patients with advanced meningitis with more neurological symptoms have higher mortality compared to non HIV TBM patients. Also starting ART prior or during TB treatment improves the outcome in HIV patients [17].

In this study, 35 (87.5%) patients were found to be anaemic in HIV positive group (p-value=0.0001) and 10 (25.0%) patients were anaemic in HIV negative group. Although we did not identify an association between anaemia and mortality, haemoglobin levels are a known risk factor for death in patients with HIV and TB infection. Haematocrit level is independently associated with death in HIV-TB co-infected patients [18,19].

Liver enzymes were raised in HIV positive patients (SGOT-50%, SGPT-22.5% with a p-value of 0.039 and 0.023, respectively) in this study. This finding was similar to the study done by Netto I et al., in which mean serum Aspartate Transaminase (AST) and Alanine Transaminase (ALT) increased from 22.15±2.67 IU/L and 17.85±1.84 IU/L respectively, to upto 95.85±26.9 IU/L (p<0.001) and 85.67±28.56 IU/L (p<0.001) in HIV positive patients [20]. The increase was found to be statistically highly significant. The derangement in serum liver enzyme level may help us identify patients requiring further investigations, and can be use a prognostic tool in HIV [21].

Hyponatremia was found in 16 (40%) HIV positive patients and 15 (37.5%) non HIV patients (p-value=0.818). According to Torok ME TBM can cause metabolic complications, especially hyponatremia, which affects >50% of patients with the disease despite normal concentrations of Antidiuretic Hormone (ADH), even though they have not ruled out the role of ADH [22]. Another study done in Cambodia, on role of hyponatremia in diagnosis of Extra-Pulmonary Tuberculosis (EPTB) in HIV positive patients have shown that 57% of patients of EPTB had hyponatremia. This study showed that hyponatremia should be considered as marker for searching evidence of EPTB in

an HIV patients [23]. TBM-associated hyponatremia have low plasma volumes and persistent natriuresisas Cerebral Salt Wasting (CSW) is one of the most common causes of hyponatremia beside Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) [24].

Raised ESR was seen in 35 (87.5%) non HIV TBM patients (p-value 0.0001), whereas it was normal in 30 (75%) HIV-TBM patients. A study conducted in India by Sarkar K et al., in 2004, showed that HIV infected TB patients have lower ESR compared to HIV negative TB patients, and concluded that low ESR in TB patients may have an association with HIV infection and higher ESR may be protective towards HIV infection in resource-poor settings like India [25].

CT brain, done on admission, showed a majority of the HIV positive patients having tuberculoma (22.5%) and basal exudates (20%) and non HIV patients had meningeal enhancement (25%). Katrak SM et al., found that meningeal enhancement and obstructive hydrocephalus was not commonly seen in TBM patients with HIV infection probably due to reduced and atypical inflammatory response in them [7]. HIV-infected individuals are also more likely to present with cerebral infarcts and mass lesions, and less likely to present with obstructive hydrocephalus [26]. MRI brain on admission showed tuberculoma (32.5%) as the most common finding in both groups. MRI has better sensitivity and can show small abnormalities in both the brain and spine. Meningeal enhancement is better visualised because of the signal contrast between the inflamed meninges and the CSF, as well as infarction, and is useful for follow-up [27].

CSF ADA >5 favouring a diagnosis of TBM was present in 32 (80%) patients in HIV positive group and 38 (95%) patients in HIV negative group. Meta-analysis (13 studies with 380 patients of TBM) of ADA values (1 to 10 IU/L) in TBM cases and controls was done by Tuon FF et al., They have observed that ADA values from 1 to 4 U/l helped to exclude TBM; values between 4 and 8 U/l were insufficient to confirm or exclude the diagnosis of TBM, and values >8 U/l improved the diagnosis of TBM [28].

Survival of the patients at 6 months was better in the HIV negative (65%) group compared to HIV positive group (55%) in our study. In a retrospective study done by Suzaan M et al., in Cape Town (SA) the incidence of 6-month mortality in HIV patients with TBM was 48% which was similar to our study [17]. The incidence of MDR-TBM was high in HIV positive (7.5%) compared to non HIV (2.5%) patients in our study. A study done in Korea by Lee S et al., showed the prevalence of 11.1% MDR-TBM in HIV patients and 8.2% in non HIV patients which was higher compared to our study [29].

Adverse effect of anti-TB treatment was found in 9 (22.5%) patients in HIV positive group and none in HIV negative group (p-value=0.001). Zhang J et al., have shown that drug-resistant TB, especially MDR-TB, was associated with long-term and complicated treatment, poor prognosis, and a severe sequel, and it also takes a huge toll on patients and medical workers [30].

The adverse effect of antiretroviral therapy was found in 4 (10%) patients in HIV positive group in the present study. A study done by Lorío M et al., reported the incidence of ADEs due to ART to be around 6.2% [31].

Limitation(s)

This was a single-institution study; a multicentre study on similar lines in the future would support and fortify the findings observed in this study; shorter follow-up of 6 months. A large follow-up could result in better data with wider applications.

CONCLUSION(S)

The HIV with TBM co-infection is associated with more severe clinical manifestations, abnormal laboratory parameters, very high incidences of complications and adverse drugs reactions to both AKT and ART as well as very high mortality. Early diagnosis and prompt initiation of treatment with anticipation of adverse events and their monitoring will ensure better management of such patients.

REFERENCES

[1] Global tuberculosis report 2021. Geneva: World Health Organization; 2021.
[2] Web Annex 1. Key data at a glance. In: Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021.
[3] Aishwarya G, Sunil PB, Kamath P, Rakesh KB, Rathi P, Jagadish S et al. A pattern of opportunistic infections among HIV in patients on antiretroviral therapy in a tertiary care hospital in coastal Karnataka: A retrospective evaluation. International Journal of Research in Pharmaceutical Sciences. 2020;11(4):6385-90.
[4] Karande S, Hupta V, Kulkarni M, Joshi A, Rele M. Tuberculous meningitis and HIV. Indian J Pediatr. 2005;72:755-60.
[5] Schutte CM. Clinical, cerebrospinal fluid and pathological findings and outcomes in HIV-positive and HIV-negative patients with tuberculous meningitis. Infection. 2001;29:213-17.
[6] El Sahly HM, Teetter LD, Pan X, Musser JM, Graviss EA. Mortality associated with central nervous system tuberculosis. J Infect. 2007;55:502-09.
[7] Katrak SM, Shembalkar PK, Bijwe SR, Bhandarkar LD. The clinical, radiological and pathological profile of tuberculous meningitis in patients with and without human immunodeficiency virus infection. J Neurol Sci. 2000;181:118-26.
[8] Puccioni-Sohler M, Brandao CO. Factors associated to the positive cerebrospinal fluid culture in the tuberculous meningitis. Arq Neuropsiquiatr. 2007;65:48-53.
[9] Bossi P, Reverdy O, Caumes E, Mortier E, Meynard JL, Meyohas MC, et al. Tuberculous meningitis: Clinical, biological and x-ray computed tomographic comparison between patients with or without HIV infection Presse Med. 1997;26:844-47.
[10] Yechoor VK, Shandera WX, Rodriguez P, Cate TR. Tuberculous meningitis among adults with and without HIV infection. Experience in an urban public hospital. Arch Intern Med. 1996;156:1710-16.
[11] Dr Meg Doherty. 2021 WHO HIV clinical and service delivery recommendations. Department of Global HIV, Hepatitis and Sexually Transmitted Infection Programmes. WHO March 2021.
[12] National Technical Guidelines on Anti-Retroviral Treatment. National AIDS Control Organization (NACO), Ministry of Health and Family Welfare Government of India. Oct 2018;1-229.
[13] Hurtado RM, Meressa D, Goldfeld AE. Treatment of drug-resistant tuberculosis among people living with HIV. CurrOpin HIV AIDS. 2018;13:478-85.
[14] Zürcher K, Ballif M, Fenner L, Borrell S, Keller PM, Gnokoro J, et al. Drug susceptibility testing and mortality in patients treated for tuberculosis in high-burden countries: A multicentre cohort study. Lancet Infect Dis. 2019;19:298-307.
[15] Marais S, Thwaites G, Schoeman JF, Török ME, Misra UK, Prasad K, et al. Tuberculous meningitis: A uniform case definition for use in clinical research. Lancet Infect Dis. 2010;10(11):803-12.
[16] Pehlivanoglu F, Kart Yasar K, Sengoz G. Tuberculous Meningitis in adults: A review of 160 cases. Scientific World Journal. 2012;2012:169028.
[17] Suzaan M, Pepper DJ, Schutz C, Wilkinson RJ, Meintjes G. Presentation and outcome of tuberculous meningitis in a high HIV prevalence setting. PloS one vol. 2011;6:20077.
[18] Croda MG, Vidal JE, Hernández AV, Dal Molin T, Gualberto FA, de Oliveira AC. Tuberculous meningitis in HIV-infected patients in Brazil: Clinical and laboratory characteristics and factors associated with mortality. Int J Infect Dis. 2010;14(7):586-91.
[19] Obirikorang C, Yeboah FA. Blood haemoglobin measurement as a predictive indicator for the progression of HIV/AIDS in resource-limited setting. J Biomed Sci. 2009;16(1):102.
[20] Netto I, Borgaonkar K, Lobo R. Aminotransferase profile in HIV positive patients. Indian J Sex Transm Dis. 2009;30(2):121.
[21] Patil R, Raghuwanshi U. Aminotransferase profile in HIV positive patients. J Pure Appl Microbiol. 2010;4(1):263-66.
[22] Torok ME. Tuberculous meningitis: Advances in diagnosis and treatment. Br Med Bull. 2015;113(1):117-31.
[23] Lynen L, Phan S, Prey SP, Sopheak T, Harwell J, Boelaert M, et al. Does Hyponatremia have a value in the diagnosis of extrapulmonary tuberculosis in HIV-1 infected patients in cambodia? The Open Infectious Diseases Journal. 2007;1:01-03.
[24] Misra UK, Kalita J. Mechanism, spectrum, consequences and management of hyponatremia in tuberculous meningitis. Wellcome Open Research. 2021;4:189.
[25] Sarkar K, Baraily S, Dasgupta S, Bhattacharya SK. Erythrocyte sedimentation rate may be an indicator for screening of tuberculosis patients for underlying HIV infection, particularly in resource-poor settings: An experience from India. Journal of Health, Population and Nutrition. 2004;22:220-21.
[26] Vinnard C, MacGregor RR. Tuberculous meningitis in HIV-infected individuals. Curr HIV/AIDS Rep. 2009;6(3):139-45.
[27] Abdelmalek R, Kanoun F, Kilani B, Tiouiri H, Zouiten F, Ghoubantini A, et al. Tuberculous meningitis in adults: MRI contribution to the diagnosis in 29 patients. Int J Infect Dis. 2006;10(5):372-77.
[28] Tuon FF, Higashino HR, Lopes MI, Litvoc MN, Atomiya AN, Antonangelo L, et al. Adenosine deaminase and tuberculous meningitis-a systematic review with meta-analysis. Scand J Infect Dis. 2010;42:198-207.

[29] Lee S, Lee SH, Mok JH, Lee SJ, Kim KH, Lee JE, et al. Is multi-drug resistant tuberculosis more prevalent in HIV-infected patients in Korea Yonsei Med J. 2016;57(6):1508-10.
[30] Zhang J, Hu X, Hu X, Ye Y, Shang M, An Y, et al. Clinical features, outcomes and molecular profiles of drug resistance in tuberculous meningitis in non HIV patients. Sci Rep. 2016;6:19072.
[31] Lorío M, Colasanti J, Moreira S, Gutierrez G, Quant C. Adverse drug reactions to antiretroviral therapy in HIV-infected patients at the largest public hospital in Nicaragua. Journal of the International Association of Providers of AIDS Care. 2014;13(5):466-70.

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