Practice Trends in Treating Central Nervous System Tuberculosis and Outcomes at a Tertiary Care Hospital: A Cohort Study of 244 Cases

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Abstract

Introduction: Tubercular meningitis (TBM) is a common cause of chronic meningitis in India; however, there is a paucity of literature on optimum duration and choice of drug therapy. **Materials and Methods:** This was an ambispective cohort study. **Results:** Two hundred and forty-four patients of central nervous system tuberculosis (CNS TB) who were seronegative for HIV were studied of whom 198 had TBM and 46 patients had tuberculoma without meningitis. Before completion of treatment, 84% of TBM patients underwent imaging. There was no difference in disability or mortality in patients, who were treated with various drug regimens in terms of duration of therapy or number of drugs at initiation of treatment. However when patients developed new complications, adding more drugs improved survival. Prolonging corticosteroid administration in patients with nonsatisfactory improvement at 8 weeks was not associated with prevention of disability. **Conclusions:** CNS TB is treated by neurologists and physicians in India, as per their experience due to different recommendations in various guidelines. There is a tendency to decide when to stop treatment based on neuroimaging given the fear of poor outcomes associated with recurrence of the disease. The duration of treatment or choice of drugs at the start of treatment did not affect disability.

Keywords: Antitubercular therapy, central nervous system tuberculosis, tubercular meningitis, tuberculoma

INTRODUCTION

Tuberculosis (TB) is a common infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis*. TB attacks the lungs as well as other parts of the body. Central nervous system tuberculosis (CNS TB) is the most severe form of TB and accounts for approximately 5%–10% of all extrapulmonary cases and around 1% of all TB cases.[1]

Despite the availability of highly efficacious treatment for decades, TB remains a major global health problem. TB is the 9th leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS.[2] Considering 10% cases as CNS TB, incidence of CNS TB in India was approximately 21.2/100,000 population/year in the year 2016.

Before the advent of effective antitubercular therapy (ATT) tubercular meningitis (TBM) was uniformly fatal. Even today, the outcome of TBM remains poor, despite the availability of highly effective chemotherapy. Many series report mortality >20% and severe neurological sequelae in approximately 30% of survivors.[3,4] There are few randomized trials in TBM comparing various drug regimens with conflicting results.[5-7] The duration of treatment for TBM have not been tested in head-to-head randomized controlled trials and is currently unknown. A recent meta-analysis compared cohorts who received 6 months of ATT with those who received longer duration regimens and found no difference in relapse rates.[8] Current guidelines for treatment of TBM are to a large extent based on the principles governing the treatment of pulmonary TB[9-16] with longer durations recommended for TBM. These guidelines acknowledge the scarcity of evidence from controlled trials. The main areas of uncertainty are in the choice of the 4th drug in the intensive phase and the composition and duration of the continuation phase. The WHO, BIS, NICE, and IDSA/ATS as well as INDEX-TB guidelines recommend treatment durations varying from 6 to 12 months [Box 1]. Due to lack of evidence from randomized controlled trials, the current duration of treatment is quite arbitrary and variable and depends on the physician's choice.

The present study was designed to evaluate the trends in management and outcomes of TBM at a tertiary level hospital.

MATERIALS AND METHODS

This was an ambispective cohort study designed according to the STROBE checklist for observational studies. The study was undertaken at a tertiary referral center in North India.

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Consecutive patients of age >12 years with a diagnosis of intracranial tubercular infection who were admitted (from emergency, neurology outpatient department) or attending the neurology outpatient department (OPD) at the All India Institute of Medical Sciences (AIIMS), New Delhi were enrolled. The study was approved by the Institutional Review Board of the AIIMS, New Delhi. Informed written consent was obtained from all patients. Patients who were diagnosed to have TBM from December 2009 to December 2011 were recruited prospectively and followed up. Those who were previously diagnosed and were attending follow-up clinics in the OPD during the same duration were also recruited and followed up until therapy was complete or death. Follow-up duration ranged from 8 to 66 months. Patients with HIV were not admitted in the neurology department and were not included in this study.

Diagnostic criteria for tuberculous meningitis
The diagnosis of TBM was based on clinical grounds and supported by imaging and cerebrospinal fluid (CSF) studies.[17] The cases were pragmatically included based on the diagnosis made by the treating physician using criteria used in various studies and after ruling out with reasonable certainty other causes of meningitis such as partially treated

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Box 1: Various society guidelines for treatment of TBM

World Health Organization (2010/2017)[9,10]
- Pulmonary and extrapulmonary TB should be treated with the same regimen
- Intensive phase therapy for 2 months with HRZE followed by a continuation phase of 4 months with HR
- In chapter 8,[9] it has been noted that some experts recommend 9-12 months of treatment for TB meningitis given the serious risk of disability and mortality
- Adjuvant corticosteroid treatment is recommended for TBM. In TBM, ethambutol should be replaced by streptomycin

IDSA/ATS[13]
- For treatment of tuberculosis of the meninges, a 9-12-month regimen is recommended
- Prolongation of therapy also should be considered for patients with tuberculosis in any site that is slow to respond

The BIS recommendations[14]
- First-line treatment regimen (HRZE) for all forms of CNS TB
- Drugs should be taken each day either individually or in combination form
- Patients should be treated for a minimum of 12 months

National institute for clinical excellence, NICE guidelines[15]
- Patients with active meningeal TB should be treated for 12 months
- HRZ and a fourth drug (for example, ethambutol) for the first 2 months
- Followed by isoniazid and rifampicin for the rest of the treatment period

Indian extrapulmonary TB (INDEX-TB) guidelines[16]
- TB meningitis should be treated with standard first-line ATT for at least 9 months

HRZE=Isoniazid, rifampicin, pyrazinamide, ethambutol, TBM=TB meningitis, TB=Tuberculosis, IDSA=Infectious Diseases Society of America, ATS=American Thoracic Society, BIS=British Infection Society, NICE=National Institute for Clinical Excellence, CNS=Central nervous system

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bacterial meningitis, viral meningoencephalitis, syphilitic, and carcinomatous meningitis. etc.

Clinical
Headache, fever, vomiting - for >5 days, stiff neck, papilledema, cranial nerve palsies, hemiparesis, and other features suggestive of meningitis.

Imaging
Computed tomography (CT) or magnetic resonance imaging (MRI) showing exudates, hydrocephalus, tuberculoma, infarcts, and contrast enhancement in meninges.

Cerebrospinal fluid
- CSF pleocytosis: >20 cells/mm^3,
- Lymphocytic or neutrophilic pleocytosis,
- Low CSF: blood sugar ratio <0.5,
- Raised protein >40 mg/dL;
- GeneXpert,
- AFB staining: optional and if available.

Supportive criteria
Extra CNS tuberculosis
The diagnosis of TBM was classified as definite, highly probable, probable, and possible based on the criteria by Ahuja *et al.*[18]

Intracranial tuberculoma was diagnosed if contrast-enhancing lesions were identified on CT scan or MRI of the brain and one or more of the following criteria:[19]
1. Clinical and/or radiographic response to ATT
2. Microbiologic, histopathologic, or radiographic evidence of active pulmonary or systemic TB
3. Histopathologic features of granulomatous inflammation of the biopsied/excised CNS lesion.

The patient's demographic and clinical characteristics were noted. Age, gender, presenting symptoms and signs, level of consciousness on Glasgow Coma Scale (GCS) at the time of presentation, blood, CSF, and imaging investigations were recorded. Patients were classified according to the Medical Research Council (MRC) grading, in which Grade I patient was alert and oriented without focal deficit, Grade II was GCS 10–14 without focal deficit or GCS 15 with focal deficit, and Grade III was GCS <10.[20]

ATT regimen and duration of treatment, imaging for follow-up were decided by the treating neurologist.

Follow-up and assessment
Patients were followed up at monthly intervals or as and when required after discharge, based on the clinical condition of the patient. The decision to image the patients at various follow-up visits and the time point of stopping treatment was decided by the treating physician based on the clinical profile of the patient as well as individual treatment practices.

Patients were followed up during the treatment period and any fresh-onset neurological complications such as hemiparesis, seizures, and need for neurosurgical interventions

like ventriculoperitoneal shunt (VP Shunt) were noted. Drug-related adverse effects such as hepatitis and ototoxicity were recorded. At the time of completion of treatment, patients' brain imaging findings (if done) along with any persistent neurological sign or symptoms (sequelae of disease) were also noted. At the completion of treatment, the outcome was assessed according to Modified Rankin Scale (mRS). mRS of ≤2 was categorized as good outcome, while 3 or more was considered to be poor outcome.

Statistical analysis

Statistical analysis was done with STATA Version 12. Data were expressed as mean and standard deviation in case of normal distribution and medians with range in case of nonnormal distribution. Difference between two groups of normally distributed variables was compared with *t*-test and nonnormally distributed variables with Wilcoxon rank-sum test. Proportions were compared using Chi-test or Fisher's exact test. Odds ratio for predictors of outcome were calculated by logistic regression analysis.

RESULTS

Two hundred and forty-four patients (124-TBM, 74-TBM with tuberculoma, and 46 only tuberculoma) were included in the study. Fever and headache were present in all cases of TBM as these were mandatory for the diagnosis of TBM according to Ahuja *et al*. Table 1 shows the demographic, clinical, and laboratory parameters of the patients with TBM.

Treatment trends

The patients were diagnosed based on clinical, imaging, and CSF findings as described above and the treatment protocol was decided by treating physicians based on their experience [Table 2]. Treatment was started as soon as the diagnosis was considered. In the intensive phase, rifampicin, isoniazid (INH), and pyrazinamide were given in all patients. Streptomycin was given in doses varying from 0.5–1 g/day for 8–12 weeks. Out of 150 patients, 140 patients were started with regimes including streptomycin and in ten patients streptomycin was added during the course of treatment. Of 113 patients, in whom data on the duration of streptomycin were available, 74 patients (65.5%) had been prescribed streptomycin for 8 weeks and 31 patients (27.4%) received it for 12 weeks. There was no difference in outcomes between patients who had received streptomycin for 8 weeks or 12 weeks. In eight patients, streptomycin was given for <8 weeks (in five patients developed ototoxicity and three patients discontinued due to intramuscular injection pain).

Forty-four patients (22.22%) developed drug-induced hepatitis (DIH), which was diagnosed when SGPT increased to ≥ three times the upper limit of normal (ULN) with symptoms of hepatitis such as nausea, vomiting, and anorexia, or 5 times the ULN without symptoms. When DIH was diagnosed, rifampicin, INH, and pyrazinamide were stopped, and at least two other drugs from two different classes (Aminoglycoside:

streptomycin, amikacin,; ethambutol and fluoroquinolone: Levofloxacin, ofloxacin, and moxifloxacin) were started. After

Table 1: Clinical profile of 198 cases of tubercular meningitis

Parameter	Observation
Sex	53% males
Age, years, mean±SD,	31±13.25; range 13-78
TBM grading (Ahuja *et al.*)	
Definite TBM, *n*(%)	2 (1)
Highly probable, *n*(%)	48 (24.24)
Probable, *n*(%)	134 (67.68)
Possible, *n*(%)	14 (7.07)
Duration of symptoms before starting treatment, days, median (range)	30 (range 14-240)
MRC Grade I, *n*(%)	43 (21.7)
MRC Grade II, *n*(%)	110 (50.5)
MRC Grade III, *n*(%)	55 (27.8)
Symptoms and signs, *n*(%)	
Anorexia	111 (57.1)
Vomiting	138 (69.7)
Extraneural TB	28 (14.1
Altered sensorium	137 (69.2)
Seizures	69 (34.4)
GCS (mean±SD)	12.42±2.97
Meningeal signs	162 (81.8)
Papilledema	96 (48.5)
Cranial nerves	93 (47) had one or more cranial nerves palsy
6th nerve	66 (33.3)
3rd nerve	32 (16.2)
4th nerve	5 (2.5)
7th nerve	3 (1.5)
Vision impairment	42 (21.2)
Optic atrophy	29 (14.6)
Investigations, mean±SD	
Hemoglobin, gm/dL±SD (range)	11.62±1.87 (7–16) 41 (28) had anemia
TLC, cells/mm3±SD (range)	8855±3095 (range 2700–19,800) 8 (5.5%) had TLC >15,000/mm³
Neutrophilic leukocytosis (>70%)	73 (56)
ESR, mm/h	26.33±14.86 (range 3–76) 34 (33) had raised ESR (>30 in 1st h)
CSF (180/198)	
Color: Clear/straw-colored turbid, *n* (%)	116 (58.6)/64 (32.3)
Cell count median (range) cells/mm³	156 (0-2400)
Acellular CSF, *n* (%)	7/180 (3.8)
<20 cells/mm³, *n* (%)	23 (11.5)
Polymorphic pleocytosis, *n* (%)	13 (7.5) had ≥50 polymorphs
Protein median (range), mg/dL	124 (range 12-3300) 29 (16) had normal protein (≤60)
Glucose median (range), mg/dL	44 (range 5-192) 50 (31) had normal CSF: Blood glucose ratio

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Table 1: Clinical profile of 198 cases of tubercular meningitis	
Parameter	Observation
Imaging	
Abnormal CXR, *n* (%)	72 (36.2)
NCCT/CECT/MRI brain (*n*=198)	
Normal, *n* (%)	20 patients (11.1)
Meningeal enhancement/ exudates, *n* (%)	144 (72.7)
Hydrocephalus, *n* (%)	116 (58.6)
Infarct, *n* (%)	53 (26.8)
Tuberculoma, *n* (%)	74 (37.4); 24 patients developed new granuloma during treatment)
Normal imaging at last follow-up (yes/no)	49/103 (All those who had normal last scan had mRS ≤3

CECT=Contrast-enhanced computed tomography, CSF=Cerebrospinal fluid, CXR=Chest X-ray, ESR=Erythrocyte sedimentation rate, GCS=Glasgow coma scale, MRC=Medical Research Council, MRI=Magnetic resonance imaging, NCCT=Noncontrast computed tomography, TLC=Total leukocyte count, TB=Tuberculosis, SD=Standard deviation

liver function tests (LFT) normalized, drugs were reintroduced one at a time usually in order of INH, rifampicin, and then pyrazinamide, while monitoring LFT on a weekly basis.

Fluoroquinolones (ofloxacin or levofloxacin) were prescribed to 58 patients (29.3%), of whom 24 patients received it as a part of modified regimen due to development of DIH. The most commonly used drug was ofloxacin (45 out of 58 patients 77.6%).

Follow-up and assessment

Patients were followed up at monthly intervals or as and when required after discharge, based on the clinical condition of the patient. Twenty-two patients out of 198 were lost to follow-up. Few patients had less frequent follow-up visits but reported to be compliant to therapy. Out of 122 patients, who completed treatment, 103 (84%) patients underwent imaging before treatment completion, of whom 49 had normal imaging and were clinically considered to be cured by the treating doctor. In 54 of them, the patients were clinically cured, however, imaging showed sequelae of TB. Only in 19 patients, the treatment was stopped without imaging as the patient was clinically cured.

Outcome of tubercular meningitis with or without tuberculoma (*n* = 198) [Table 3]

Overall, 32 (16.2%) patients with TBM died during the course of treatment. Twenty-two patients were lost to follow-up and 22 were still on therapy at last follow-up. Of the remaining 154 patients, 85 (55%) patients had good outcome (mRS ≤ 2) and 69 (45%) patients had a poor outcome (mRS ≥ 3) (18 patients were completely dependent for their activities of daily living [mRS = 4,5] and 32 patients died, mRS = 6). In 77% patients, there were sequelae of the disease and only 23% were symptom free. Outcomes of the

Table 2: Treatment regimens used in patients of tubercular meningitis with or without tuberculoma (*n*=198)	
Treatment	*n* (%)
5 drug ATT intensive phase	54 patients (27.3)
4 drugs intensive phase	144 patients (72.7)
HRZS	88 patients (44.4)
HRZE	56 patients (26.8)
Received streptomycin	150 patients (75.8)
Continuation phase	
HRZE	25 patients (20.5)
HRZ	73 patients (59.8)
HR	23 patients (17.2)
HRE	Three patients received HRE during full course as pyrazinamide stopped in the middle of intensive phase
Steroids	185 patients (93.4)
Duration weeks, median (range)	8 weeks (range 3–60 weeks) (83≤8 weeks; 75>8 weeks)
Steroids restarted after stopping, *n*(%)	48 patients (24.2)
	17 patients: Development of hydrocephalus
	10 patients: Infarct
	10 patients: Increase in tuberculoma size or new tuberculoma/abscess formation
Ventriculoperitoneal shunt, *n*(%)	45 (23)
Duration of treatment	
Months, median (range)	18 (8-66)
Duration ≤9 months	1 patient (0.82)
Duration 10-12 months	23 patients (18.85)
13-18 months	66 patients (54.10)
19-24 months	21 patients (17.21)
>24 months	11 patients (9)

Duration of treatment	TBM	TBM + tuberculoma
Months median (range)	17 (8–50)	18 (10-66)
Duration ≤9 months	1 (1.43))	0 (0)
Duration 10-12 months	15 (21.43)	8 (15.38)
Duration 13-18 months	46 (65.71)	20 (38.46)
Duration 19-24 months	5 (7.14)	16 (30.77)
Duration >24 months	3 (4.29)	8 (15.38)

ATT=Antitubercular therapy, HRZE=Isoniazid, rifampicin, pyrazinamide, ethambutol, HRZS=HRZ + streptomycin, HRE=HR + ethambutol, TBM=Tubercular meningitis

patients at the end of treatment are mentioned in Table 3. Complications associated with tubercular meningitis have been enumerated in Box 2.

Risk factors for death

Table 4 compares patients who survived and those who died. On univariate analysis, MRC grade at presentation, presence of hydrocephalus, usage of second-line ATT drugs, and total number of drugs used during treatment were found to be predictors of death. More patients who received five or more drugs during treatment survived as compared to those who received four drugs, while there was no difference in survival

Table 3: Outcome at last follow-up

Outcome	Number of patients (%)
Completed treatment	122 patients (61.6)
Died	32 patients (16.2)
On treatment	22 patients (11.1)
Lost to follow-up	22 patients (11.1)
mRS ≤2 at end of treatment	85 (55)
mRS ≥3 at end of treatment	69 (45)
Completely symptom free at end of treatment mRS=0	36 patients (23.4)
Visual impairment	22 patients (17.9)
Cranial nerve palsy	21 (17.2)
Hemiparesis	25 (20.7)
Paraparesis	23 (18.9)

mRS-Modified Rankin scale

Box 2: Complications

Hydrocephalus requiring ventriculoperitoneal shunt

- 45 patients required VP shunt due to development of severe hydrocephalus
- 21 patients were MRC Grade III, 20 patients were MRC Grade II, and 3 patients were MRC Grade I at presentation
- 25 completed therapy, 11 patients died, 5 were lost to follow-up, and 4 patients were still on treatment
- Need for VP shunt was significantly more common in patients with higher MRC grade at presentation (P=0.002)
- Out of 36 patients who needed VP shunt (completed therapy or died), 50% had poor outcome. Considering all 154 patients (completed therapy or died), 18 out of 104 patients with good outcome went through VP shunt surgery and 18 out of 50 patients with poor outcome required VP shunt surgery
- Need for VP shunt was associated with poor outcome (P=0.014)

Hemiparesis

- 46 patients developed hemiparesis
- 26 completed the therapy, 11 patients died, 2 lost to follow-up, and 7 patients were still on treatment
- 38 patients developed hemiparesis due to fresh-onset infarct (documented by CT head) and 8 had hemiparesis due to tuberculoma
- 27 patients (58.7%) had right-sided and 17 patients had left-sided hemiparesis
- 26 patients were MRC Grade III, 18 patients were Grade II, 2 patients were Grade I at presentation
- Hemiparesis was significantly more common in higher MRC grade at presentation (P<0.0001)
- Out of 37 patients of hemiparesis (completed therapy or died), 18 (48.6%) had poor outcome
- Of 154 patients who completed therapy or died, 19 out of 104 patients with good outcome had hemiparesis and 18 out of 50 patients with poor outcome had hemiparesis (P=0.026)

Arachnoiditis and paraplegia

- 29 (14.6%) patients developed arachnoiditis (documented on MRI spine)
- 33 (16.7%) patients had symptomatic weakness in both lower limbs either due to severe arachnoiditis, intradural lesion, or due to Pott's spine leading to compressive myelopathy
- Arachnoiditis and paraparesis were also associated with poor outcome (P=0.001 and 0.002, respectively)

Movement disorder

- 9 patients (4.5%) had movement disorders during the study period
- Three patients had rubral tremor and one patient had thalamic tremor, which were well correlated with midbrain and thalamic infarct
- One patient developed chorea after basal ganglia infarct
- One patient developed upper limb dystonia due to brainstem infarct
- Three patients developed Parkinsonian symptoms as slowness, cogwheel rigidity, and resting tremor, but these patients had no focal basal ganglia lesion
- One patient had hemifacial spasm on treatment, which could have been incidental

Drug-induced hepatitis

- 44 patients developed DIH
- Out of these 44 patients, 29 completed the therapy, 10 patients died, 1 lost to follow-up, and 4 patients are still on treatment
- DIH was not associated with increased mortality on multivariate analysis but not associated with increased disability

DIH=Drug-induced hepatitis, MRC=Medical Research Council, VP=Ventriculoperitoneal

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in patients, who were started on four drugs or five drugs. This is because, the patients who had severe disease as assessed during treatment course or who developed complications such as infarct, worsening of hydrocephalus, and new or increasing granulomas were treated by adding drugs during the treatment course and then they survived. This is reflected from the fact that usage of second-line drugs was associated with increased survival.

Patients who presented with higher MRC grade at treatment initiation had 3.97 times higher odds of death. [95% CI 1.98-7.95; P <0.001]. Adjusted odds ratio for death was 5.02 (95% CI: 2.26–11.19) for higher MRC grade at presentation after adjusting for age, duration of symptoms before starting treatment, presence of hydrocephalus, total number of drugs used, and occurrence of drug-induced hepatitis. MRC grade at presentation [Odds ratios [OR]: 4.92; (95% CI: 2.18–11.11)], occurrence of DIH [OR: 3.72; 95% CI: 1.21–11.47] and usage of the second-line drugs [OR: 8.87; 95% CI: 2.45–32.1] were found to be independent predictors of death on multivariable analysis adjusting for age, duration of symptoms before treatment initiation, and presence of hydrocephalus.

Risk factors for poor outcome

Table 5 compares patients with good (mRS ≤2) and poor (mRS ≥3) outcomes. On univariate analysis, higher MRC grade at presentation, presence of sixth nerve palsy, meningeal enhancement, hydrocephalus, VP shunt insertion, and duration of corticosteroid administration were found to be associated with poor outcome. Corticosteroid administration was prolonged in patients who did not show desired improvement and the median duration of corticosteroid administration was 8 weeks (3–52 weeks) in those with good outcome and 12 weeks (4–60 weeks) in those with poor outcome. However, increased duration of corticosteroid administration, however, did not improve the outcome. It was observed that of the patients who had hydrocephalus at presentation who had completed treatment (96/154), 36 underwent ventriculoperitoneal shunting (14/71 [16%] of patients with good outcome and

Table 4: Differences between patients who completed therapy versus died

	Completed therapy (*n*=122)	Died (*n*=32)	*P*
Age (years mean±SD)	31.66±14.04	32.56±13.61	0.746
Male, *n*(%)	60 (81)	14 (19)	0.584
Female, *n*(%)	62 (78)	28 (22)	
TBM/TBM + tuberculoma, *n*(%)	70/52 (57/43)	23/9 (72/28)	0.136
Definite, *n*(%)	0 (0)	1 (3)	0.110
Highly probable, *n*(%)	30 (25)	7 (22)	
Probable, *n*(%)	82 (67)	24 (75)	
Possible, *n*(%)	10 (8)	0 (0)	
Duration of disease, days, median (range)	30 (14–240)	37.5 (15–150)	0.70
Pulmonary Koch's, *n*(%)	46 (38)	14 (44)	0.533
MRC grade, *n*(%)			
I	30 (25)	0 (0)	<0.001
II	63 (52)	14 (44)	
III	29 (24)	18 (56)	
GCS, median(range)	14 (6–15)	10 (3–15)	<0.001
Papilledema, *n*(%)	59 (77)	18 (23)	0.552
Seizure (yes/no) (%)	43/79 (35/65)	17/15 (53/47)	0.710
Visual impairment (%)	29 (24)	3 (9)	0.09
Cranial nerve palsies (%)	55 (45)	19 (60)	0.15
Hemiparesis (yes/no) (%)	26/96 (21/79)	11/21 (34/66)	0.124
Paraparesis (yes/no) (%)	24/98 (20/80)	5 (16/84)	0.800
Arachnoiditis (yes/no) (%)	21/101 (17/83)	4/28 (12.5/88)	0.520
Meningeal enhancement/exudates (yes/no) (%)	90/32 (74/26)	27/5 (84/16)	0.211
Hydrocephalus (yes/no) (%)	70/52 (57/43)	26/6 (81/19)	0.013
Infarct (yes/no) (%)	31/91 (25/75)	13/19 (41/59)	0.09
Tuberculoma (yes/no) (%)	53/69 (43/57)	8/24 (25/75)	0.058
CSF			
Color-yellowish or turbid, *n*(%)	37 (73)	14 (27)	0.405
Total white cell count/ml (median) (range)	150 (0–1945)	190 (0–2400)	0.50
Protein (median) (range) mg/dL	115 (12–2000)	153 (22–3300)	0.11
Sugar (median) (range) mg/dL	43 (5–139)	37 (7–192)	0.59
CSF: Blood sugar ratio (median) (range)	0.4 (0.04–0.88)	0.33 (0.06–0.96)	0.25
Ventriculoperitoneal shunt (yes/no), *n*(%)	25/97 (20/80)	11/21 (34/66)	0.099
Number of drugs started (4/5), *n*(%)	88/34 (72/28)	26/6 (81/19)	0.30
Total no of drugs used	n=117	n=32	
4 drugs, *n*(%)	57 (69.5)	25 (30.5)	0.008
5 drugs, *n*(%)	37 (90.24)	4 (9.76)	
>5 drugs, *n*(%)	28 (90.32)	3 (9.68)	
Streptomycin (+), *n*(%)	91 (75)	27 (84)	0.348
Streptomycin (-), *n*(%)	31 (25)	5 (16)	
Drug-induced hepatitis (yes/no)	29/93 (24/76)	10/22 (31/69)	0.387
Second-line drugs used (yes/no)	51/71 (42/58)	4/28 (12.5/87.5)	0.002
Steroids duration weeks (median, range)	9.5 (3–52)	12 (4–60)	0.60
Steroids ≤8 weeks, *n*(%)	53 (45)	5 (56)	0.731
Steroids >8 weeks, *n*(%)	64 (55)	4 (44)	
Restarted steroids (yes/no(%))	34/88 (28/72)	6/26 (19/81)	0.30

CSF=Cerebrospinal fluid, GCS=Glasgow coma scale, MRC=Medical research council, TBM=Tubercular meningitis

22/47 [32%] patients with poor outcome). Patients underwent surgery because of deterioration in sensorium or progressive increase in hydrocephalus in spite of best medical therapy. This emphasizes the importance of MRC grade in predicting outcome. On multivariate analysis, MRC grade was the only variable associated with poor outcome after correcting for age, duration of symptoms before treatment initiation, presence of sixth nerve palsy, number of drugs used, usage of second-line drugs, as well as duration of treatment or occurrence of DIH. Patients who had higher MRC grade at presentation had 2.57 times higher odds of poor outcome (95% CI: 1.5–4.4) after adjusting for above factors.

Table 5: Comparison between patients with good and poor outcome

	mRS ≤2 (85)	mRS ≥3 (69)	*P*
Age (years, SD)	31.16 (14.58)	32.7 (13.1)	0.50
Sex (male/female) *n*(%)	40/45 (47/53)	34/35 (49/51)	0.784
TBM/TBM + tuberculoma (%)	51/34 (60/40)	42/27 (61/39)	0.913
Definite/highly probable	20	18	0.069
Probable	56	50	
Possible	9	1	
Duration of illness Days median (range)	30 (14–240)	30 (14–180)	0.78
Pulmonary involvement, *n*(%)	30 (35)	30 (43)	0.3
MRC at presentation, *n*(%)			
Grade I	23 (27)	7 (10)	<0.001
Grade II	47 (55)	30 (43)	
Grade III	15 (18)	32 (46)	
GCS, median(range)	15 (6–15)	11 (3–15)	<0.001
Papilledema (yes/no) (%)	41/44 (48/52)	36/33 (52/48)	0.627
Seizure (yes/no) (%)	30/55 (35/65)	30/39 (43/57)	0.300
Visual impairment (yes/no) (%)	15/70 (18/82)	17/52 (25/75)	0.29
Sixth nerve palsy (yes/no) (%)	24/61 (28/72)	30/39 (43/56)	0.049
Hemiparesis (yes/no) (%)	15/70 (18/82)	22/47 (32/68)	0.040
Paraparesis (yes/no) (%)	5/80 (6/94)	24/45 (35/65)	<0.001
Arachnoiditis (yes/no) (%)	4/81 (5/95)	21/48 (30/70)	<0.001
Imaging, *n*(%)			
Meningeal enhancement	59/26 (69/31)	58/11 (84/16)	0.034
Hydrocephalus (yes/no) (%)	47/38 (55/45)	49/20 (71/29)	0.045
Infarct (yes/no) (%)	17/68 (20/80)	27/42 (39/61)	0.009
Tuberculoma (yes/no) (%)	35/59 (41/59)	26/43 (38/62)	0.659
CSF			
Yellowish or turbid, *n* (%)	48 (63)	40 (63)	0.968
TLC/ml median (range)	145 (0–1945)	156 (0–2400)	0.623
Protein median (range)	113 (13–1000)	139 (12–3300)	0.339
Sugar median (range)	43.5 (5–110)	7 (40–192)	0.708
CSF: Blood sugar ratio median (range)	0.39 (0.04–0.88)	0.38 (0.06–0.96)	0.920
Ventriculoperitoneal shunt (yes/no) (%)	14/71 (16/84)	22/47 (32/68)	0.025
Total number of drugs 4/5/>5			
4 drugs, *n*(%)	43 (50.59)	39 (56.52)	0.257
5 drugs, *n*(%)	27 (31.76)	14 (20.29)	
>5 drugs, *n*(%)	15 (17.65)	16 (23.19)	
Streptomycin (+), *n*(%)	63 (74)	55 (80)	0.415
Streptomycin (-), *n*(%)	22 (26)	14 (20)	
Drug induced hepatitis (yes/no) (%)	23/62 (27/73)	16/53 (23/77)	0.583
Treatment duration, months (range)	18 (8–60)	18 (11–66)	0.816
Duration (<9 months), *n*(%)	1 (1.18)	0 (0)	
Duration (9–12 months), *n*(%)	14 (16.47)	9 (24.32)	0.230
Duration (13–18 months), *n*(%)	49 (57.65)	17 (45.95)	
Duration 19–24 months), *n*(%)	16 (18.82)	5 (13.51)	
Duration (>24 months), *n*(%)	5 (5.88)	6 (16.22)	
Second-line drugs used, *n*(%)	32/53 (38/62)	23/46 (33/67)	0.578
Steroids duration weeks, median(range)	8 (3–52)	12 (4–60)	0.0315
Steroids ≤8 weeks, *n*(%)	43 (53)	15 (33)	0.033
Steroids >8 weeks, *n*(%)	38 (47)	30 (67)	
Restarted steroids, (yes/no) (%)	22/63 (26/74)	18/51 (26/74)	0.977

CSF=Cerebrospinal fluid, GCS=Glasgow coma scale, MRC=Medical Research Council, mRS=Modified Rankin scale, TBM=Tubercular meningitis, GCS=Glasgow coma scale, TLC=Total leukocyte count, SD=Standard deviation

Table 6: Presenting features, treatment patterns, and outcomes of tuberculoma without meningitis

Presenting feature	Number of patients	Total number	Percentage
Fever	12	46	26.09
Headache	24	46	52.17
Vomiting	13	46	28.26
Anorexia	5	46	10.87
Meningeal signs	1	46	2.17
Papilledema	6	46	13.04
Seizure	37	46	82.22
Number of lesions	**Number of patients**	**Total number**	**Percentage**
1	17	46	36.96
2	1	46	2.17
3 or more	28	46	60.87
Treatment regime, *n*(%)	**mRS ≤2**	**mRS ≥3**	***P***
HRZES	4 (10.26)	1 (16.67)	0.395
HRZE	19 (48.72)	5 (83.33)	
HRZS	12 (30.77)	0 (0)	
HRZL	1 (2.56)	0 (0)	
HRZ	3 (7.69)	0 (0)	
Duration of treatment, *n*(%)	**mRS ≤2**	**mRS ≥3**	***P***
9 months	1 (2.56)	0 (0)	0.868
10-12 months	3 (7.69)	0 (0)	
13-18 months	15 (38.46)	2 (50)	
19-24 months	15 (38.46)	1 (25)	
25-30 months	4 (10.26)	1 (25)	
36 months	1 (2.56)	0 (0)	
Steroids (*n*)	33	46	71.74
Drug-induced hepatitis (*n*)	11	46	24.44
Imaging at last follow-up, *n*(%)	**Number of patients**	**Percentage**	***P***
Normal	13 (35.14)	1 (33.33)	>0.999
Lesion size decreased but persisting	9 (24.32)	1 (33.33)	
Calcified lesion	13 (35.14)	1 (33.33)	
Gliotic lesion	2 (5.41)	0 (0)	

HRZE=Isoniazid, rifampicin, pyrazinamide, ethambutol, HRZES=HRZE + streptomycin, HRZL=HRZ + levofloxacin

Tuberculoma without meningitis

46 patients had intracranial tuberculoma without evidence of meningitis. Tubeculoma was diagnosed using criteria mentioned in the methods section of this article. The most common presentation was with seizures. The proportion of patients who had various clinical features is detailed in Table 6. Only 3 patients (6.5%) had sixth nerve palsy. 11 patients (23.9%) had hemiparesis during course of illness. Pulmonary involvement was found in 11 patients (23.9%).

The various treatment regimens, outcomes, and findings on imaging at last follow-up have been mentioned in Table 6. It is of importance to note that, only one patient had increase in lesion size on follow-up imaging after stopping treatment. This patient had multiple granulomas and received 22 months of treatment (3 months of streptomycin, 22 months of INH and rifampicin, 18 months of pyrazinamide, and 12 months of ethambutol). Imaging showed persistent lesion which had decreased in size when treatment was stopped due to clinical and radiologic improvement. ATT was restarted and given

for 10 months at last follow-up and the patient was still under follow-up.

DISCUSSION

Despite TBM being such a prevalent disease in India, very few studies have addressed the issue of optimal drugs and duration of treatment. Most of the published studies are in pediatric population. Even different guidelines are discordant regarding duration of treatment in CNS TB. The INDEX-TB guidelines recommend treatment for a period of at least 9 months.

The duration and number of drugs prescribed have important implications on treatment compliance as increasing number of drugs or duration of treatment increases the costs, without definite additional benefit and likely to cause more adverse effects or lead to drug resistance. Although streptomycin is the most effective bactericidal drug, route of administration (intramuscular) may be a limiting factor leading to poor compliance.

Imaging was abnormal in most of the patients (89.9%) at start of treatment. Hydrocephalus (58.6%) and meningeal enhancement or exudates (73.6%) were the most common findings and tuberculoma and infarct was seen in 36.8% and 26.8%, respectively. This is in keeping with previous reports, where hydrocephalus, basilar enhancement, infarction, and tuberculoma were the most frequently reported findings on CT examination.[21,22] In our study, 50% of those who required VP shunt due to development of severe hydrocephalus had poor outcome which is similar to that in previous studies.[23,24]

All patients received at least 4 drugs as initial therapy and HRZS (44.55%) was the most commonly prescribed combination. Majority of patients received streptomycin in intensive phase of therapy (75.8%). The proportion of patients with good outcome was comparable whether intensive phase therapy was taken for 2 or 3 months or all drugs were continued for >12 months, streptomycin was used or not, duration of therapy was 12 months or more. None of the patients in present study was on alternate day DOTS (Directly observed treatment short course) regimen of ATT.

Previous studies on treatment for TBM have reported effective duration of treatment from 6 months to 24 months and 3–4 drugs given for intensive phase and 2–3 drugs in continuation phase with varying results – some showing better results with short course of therapy and some the contrary.[3,25-32]

Overall, 16.5% patients died on treatment in our study. Mortality due to TBM has been reported from 8.3%[29] to as high as 64%[33] in different studies. Mortality was highest (38.5%) in patient presented with MRC Grade III compared to no death in MRC Grade I group, which is similar to other studies.

We found that higher MRC grade at presentation, presence of hydrocephalus were associated with increased mortality, while usage of second-line ATT drugs and usage of 5 or more drugs was associated with decreased mortality. More patients who received 5 or more drugs during treatment survived as compared to those who received 4 drugs, while there was no difference in survival in patients who were started on 4 drugs or 5 drugs. This is because, patients who had severe disease as assessed during treatment course or who developed complications such as infarct, worsening of hydrocephalus, and new or increasing granulomas, were treated by adding drugs during the treatment course and then they survived. This is reflected from the fact that usage of second-line drugs was associated with increased survival. There was no difference in mortality in patients who received 12 months or longer duration of therapy.

Corticosteroid administration was prolonged in patients who did not show desired improvement and the median duration of corticosteroid administration was 8 weeks (3–52 weeks) in those with good outcome and 12 weeks (4–60 weeks) in those with poor outcome. However, it is difficult to comment if increased duration of corticosteroid administration did not improve the outcome. Some patients who did not have significant improvement after 8 weeks of therapy improved after longer duration of steroid administration. Recommendations to prolong or stop steroid at 8 weeks cannot be made based on the available data. On multivariate analysis, MRC grade was the only variable associated with poor outcome after correcting for age, duration of symptoms before treatment initiation, presence of sixth nerve palsy, number of drugs used, usage of second-line drugs, as well as duration of treatment or occurrence of DIH.

Previous studies, in which multivariable logistic regression analysis was applied; age, poor GCS, leukocytosis, and focal weakness were found to be independent predictor of poor outcome.[34,35] There was no difference in the good outcome or the complication rate of patients who received treatment with different regimes (shorter or long duration, 4 or 5 drugs, HRZS, or HRZE had similar outcomes) with limitation of this study being an observational study.

Like any observational study, this study also has few shortcomings. All consecutive patients were enrolled in this study but 22 patients lost to follow-up and 22 were still on treatment. Hence, final analysis has been done with 154 patients of TBM. The study had retrospective (data retrieved from records) as well as prospective cases. There must have been admission bias as this study was done at tertiary level center, so less severe cases may not have been admitted and these patients might have been missed from enrolment. As each patient were following with respective physician, who had seen them first, the treatment protocol varied and minor complications, drug default, etc., might have been reported poorly.

Conclusions

Our study found that neurologists tend to image patients frequently before stopping therapy for TBM which leads to prolongation of therapy up to 66 months in some cases though guidelines recommend 12 months of therapy and no specific recommendation for imaging. There was variation in treatment protocol, though the outcomes were comparable in terms of treatment duration. In patients who developed new complications, adding more drugs to the regimen was associated with reduced mortality. In patients with inadequate improvement, prolonging the duration of corticosteroid administration was not associated with better outcomes. There is need for randomized controlled trails to establish these unresolved issues and to provide treatment guidelines to the treating doctor.

Conflicts of interest
There are no conflicts of interest.

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