ORIGINAL RESEARCH PAPER

Pulmonary Medicine

DECODING TUBERCULOUS MENINGITIS: A COMPREHENSIVE CLINICORADIOLOGICAL AND MICROBIOLOGICAL PROFILE AT A TERTIARY CARE CENTRE IN MUMBAI

KEY WORDS: Tuberculous Meningitis, Mri, Drug Resistance,mgit.

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ABSTRACT

Background: Tuberculous meningitis (TBM) is the most severe form of extrapulmonary tuberculosis and is associated with considerable morbidity and mortality. Early recognition is challenging because clinical manifestations are often nonspecific, while microbiological confirmation remains difficult.**Objective:**To evaluate the clinico-radiological and microbiological characteristics of patients diagnosed with TBM with its drug-resistance patterns.**Methodology :**This cross-sectional observational study included patients aged 12 years or older with clinically suspected or confirmed TBM cases between March and December 2016. Demographic characteristics, clinic-radiological findings, cerebrospinal fluid parameters, microbiological investigations, and outcomes were recorded prospectively and analyzed descriptively.**Results:** A total of 53 suspected TBM patients were included.With the mean age of 28.75 years predominance of female patients(71.5%) observed. Fever and headache were the most frequent presenting symptoms and meningeal enhancement(87%) commonly observed. Drug resistant cases(43.4%) were observed with high culture positivity in CSF MGIT culture of CSF. **Conclusions :** As TBM continues to present with diverse clinical and radiological manifestations, emphasizing the importance of maintaining a high index of suspicion in endemic settings with Integration of neuroimaging and microbiological testing facilitates diagnosis of drug-resistant cases at an earlier stage.

INTRODUCTION

Tuberculosis meningitis (TBM) is caused by Mycobacterium tuberculosis and is the most common form of central nervous system (CNS) tuberculosis (TB). TBM is associated with a high frequency of neurologic sequel and mortality if not treated promptly[1].TBM is the most devastating manifestation of TB and it continues to be an important cause of neurologic handicap in resource-poor countries[2]. The disease occurs when subependymal or subpial tubercles which are known as Rich foci seeded during bacillemia of primary infection or disseminated disease, rupture into the subarachnoid space. Individuals with increased risk for TBM include young children with primary TB and patients with immunodeficiency caused by aging, malnutrition, or disorders such as HIV and cancer[3].TBM is typically a subacute disease. In one seminal 2 review, symptoms were present for a median of 10 days (range, one day to nine months) before diagnosis[4].

TBM has been associated with 30% mortality in the most severe forms; moreover, 50% of survivors have neurological sequelae despite apparently adequate administration of antibiotics. Early diagnosis and prompt treatment are crucial for reducing the risk of a negative outcome. Initial signs and symptoms of disease are non-specific and the suspicion of TBM usually arises only some days or weeks after the disease's onset[2].TBM is more easily suspected when these symptoms are associated with a history of recent contact with a case of documented TB or when, after the first days of disease, relevant neurological manifestations, such as cranial nerve palsy occur[4].

Drug-resistant tuberculous meningitis is a serious and increasingly widespread clinical problem. The challenge is to detect drug-resistant disease quickly enough to start alternative drugs and thereby prevent death[5]. MDR-TB is caused by Mycobacterium tuberculosis (M. tuberculosis) resistant to both isoniazid and rifampin. Extensively drug-resistant (XDR)-TB is additionally resistant to a fluoroquinolone and an injectable second-line anti-TB medication[6]. TBM is usually paucibacillary , microbiologic diagnosis occurs in only 20-40% of cases with evidence of disease[5]. The diagnosis of TBM remains problematic despite many significant advances in diagnostic techniques, and treatment has become more challenging because of the emergence of Human Immunodeficiency Virus (HIV) and drug-resistant strains of Mycobacterium tuberculosis (MTB). Pattern of drug resistance in TB is evolving with very few data available in TBM drug resistance. With the availability of GeneXpert and MGIT DST the diagnosis of drug resistant strain is increasing day by day[7].

Mumbai bears a disproportionate burden of TB & Drug Resistant TB in India. Even though Mumbai is 1% population of country it has 2% of the total TB cases and about 11.5% of total MDR-TB cases registered in country.

This study aims at finding the resistance pattern and clinical profile of patient with TBM in Drug Resistant Hotspot, Mumbai

Aims and objectives:

Study of demographic, clinical, radiological features and outcomes also determine Drug Resistance Patterns in patients with Tuberculosis Meningitis at a tertiary care centre in Mumbai.

Materials and methods :

Study Area: This study was a prospective, cross sectional study conducted at the Pulmonary Medicine Department at tertiary care hospital, Mumbai from March 2016 to December 2016. The study was approved by the ethics committee and institutional review board.

Eligibility Inclusion Criteria: Diagnosed or clinically suspected patients of tuberculosis meningitis of age : ≥ 12 years who visited the outpatient or inpatient department on basis of clinical/radiolological/CSF analysis/microbiological investigations and were initiated on antituberculosis treatment for TBM.

Exclusion Criteria: 1. Pregnant patient. 2. HIV positive patients.

Those who met inclusion and exclusion criteria were informed about the study and written inform consent was taken.

Data collection:

A standardized proforma of the assessment including demographic details, past and present TB history, clinical Features, clinical examination, radiology, CSF analysis,

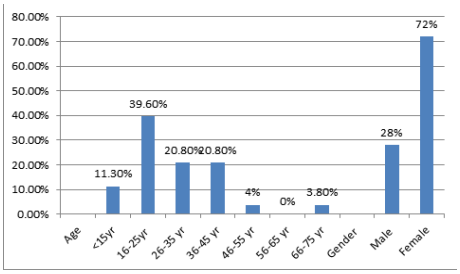
microbiology including resistance pattern and outcome assessment by Modified Rankin Scale (MRS) was completed at visit. History of co morbidities, hospitalizations and any intervention or surgery required was also noted. All investigations were performed as per standard TB care.

Sample Size: The sample size for this study was considered as a minimum of 30 patients. The sample size was determined using "Sample Size Calculator – the Survey System". Total no. of cases per month approx: 4-5 Duration of the enrolment period: 7 months Therefore total population under study (N) = 32 Considering, Confidence level = 95% Margin of Error (c) = 4% Response Distribution (P) = 50% Predicted Sample Size n (adj) = 30. Formula: n = (Z2× P (1 – P)) / c2 = (1.962× 0.5(1 – 0.5)) / 0.042 n = 600 Where Z = 1.96 for 95% CI P is expected true proportion For finite population correction; n is adjusted n (adj) = (Nxn) / (N+n) = (32x600) / (32+600) = 30.

Statistical Analysis:
Data recording was done using MS Excel. In the study descriptive statistics of various parameters had been calculated. The descriptive statistics included clinical findings, CSF findings, MRI findings, outcome, assessment of the therapy (clinical& radiological), treatment provided, and surgery status. Data was grouped on the basis of sensitive TBM, resistant TBM and probable TBM. Sub group data analysis was done using Chi-square test. Graphical representations were done wherever applicable. A p value of < 0.05 was considered statistically significant.

RESULTS :
A total of 53 patients with Tuberculosis Meningitis were included in the study. Data from 53 patients was analyzed.

Figure 1. Age and gender distribution of TBM cases



In this study ,15 (28.5%) were males and 38(71.5%) were females while mean age of the 53 patients analyzed was 28.75 ±13.30 years.

Past history of tuberculosis:
In our study 24/53(45.3%) patients had a past history of tuberculosis (9 pulmonary, 8 extrapulmonary, and 7 patients had both) while 28 (52%) had history of contact with PTB patients.

In past TB positive patients 1(4.17%) patient had proven drug susceptible TB and 3(12.5%) patients had drug resistant TB, while the rest (80%) were not aware of their drug susceptibility patterns

Co morbidities
Among these patients the most common co-morbidity observed was diabetes which affected 18% (10 patients) of the population. Ischemic heart disease was present in 11.3% (6 patients) and hypertension in 7(13.2%). Other co morbidities included Rheumatoid Arthritis, Chronic kidney disease, Scleroderma, and Parkinson's disease in 2,3,1,1 patients respectively.

Table 1: Clinical features of TBM cases

Symptoms	Total (n=53)	%
Fever	51	96.2
Headache	51	96.2
Vomiting	36	67.9
Vision changes	32	60.4
Seizure at presentation	44	83.0
Altered mentation	33	62.3
Confusion	27	50.9
Cough	30	56.6
Loss of appetite	50	94.3
Weight loss	37	69.8
Neck stiffness	29	54.7
Coma	27	50.9
Cranial nerve palsy	16	30.2
Paresis	25	47.2

Concomitant Tuberculosis at other sites:
In our cohort, 32(62%) patients had concomitant pulmonary TB, 24(45.3%) patients had military TB, 6(11.3%) patients had pleural TB, 17(32.1%) patients had lymph node TB, 7(13.2%) patients had abdominal, 8(15%) patients had spine TB and 4 had other site involvement which included knee effusion, osteomyelitis and cold abscess

Figure 2: MRI findings of TBM cases

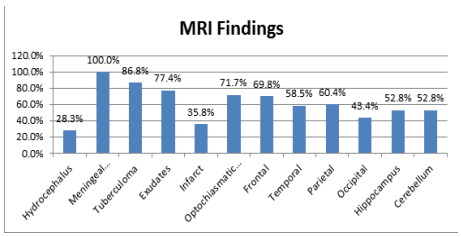


Figure 3: CSF study parameters

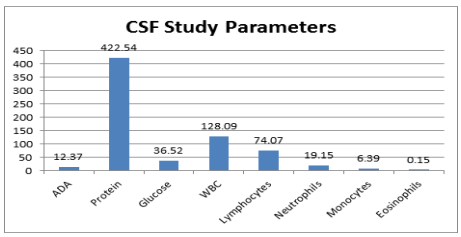
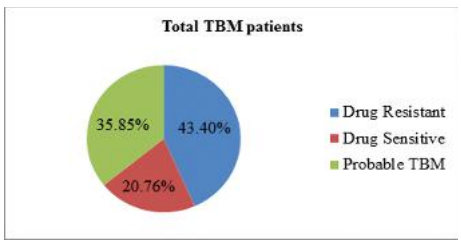


Table 2: Microbiology of CSF: AFB smear, GeneXpert and TB MGIT culture

Smear Positive for AFB	**7**
MGIT TB Culture Positive	28
Gene Xpert MTB Detected Rifampicin sensitive	3
Gene Xpert MTB Detected Rifampicin Resistant	19

Of the 53 patients in our cohort, 34 had microbiological proof of TB with one or more tests. Out of which maximum positivity detected in TB MGIT culture

Figure 4: Drug Susceptibility Pattern in total TBM patients:



DISCUSSION
Tuberculosis meningitis is the most severe form of tuberculosis and causes death or severe neurological defects in more than half of affected patients, despite advancements in antituberculosis treatments[8,9]. So,early identification of TBM is crucial for treatment success.

The presence of concomitant diseases in TBM patients contributes to diversity in the patients' clinical manifestations

and the results of laboratory examinations of cerebrospinal fluid (CSF) and cerebral Computed Tomography/Magnetic Resonance Imaging (CT/MRI). The diagnosis of TBM remains problematic despite many significant advances in diagnostic techniques. Treatment has become more challenging because of the emergence of Human Immunodeficiency Virus (HIV) and drug-resistant strains of Mycobacterium tuberculosis (MTB)[9,10]. TBM continues to be a serious problem for physicians because it is difficult to make an early diagnosis and the consequences of delaying treatment are severe[10].(71)

In the absence of a specific diagnostic method, the diagnosis of TBM is currently based mainly on the clinician's experience and a laboratory investigations[11,12]. Therefore, understanding the characteristics of TBM is very important for the diagnosis of this disease.

In our study 53 patients of TBM were analyzed for demographics, clinical features, MRI findings, CSF analysis, microbiology, resistance pattern and outcome (Figure no.1). There were a higher percentage of females (71.5%). These findings are contrary to most other Indian studies which have reported male predominance[7,13,]. However, a few studies have reported female predominance as seen in our study[14-16].

The average age of our study population was found to be 28.75 ±13.30 years. Most of the patients were between 16 to 25 years of age (39.6%). Our cohort was slightly younger as compared to the other studies which reported an average age ranging from 25 – 45 years[7,13,15].

In our study, 24 patients (45.2%) had a past history of tuberculosis. Zhang et al and Pehlivanoglu et al reported an incidence of 26% and 27% respectively[7,3] while Patel et al reported 73%.[14](135) Higher rates in our cohort is compatible with high rates of MDR-TB observed since past history of TB is a known risk factor for resistant TB

In our study most common co morbidity observed was diabetes in 10 (18%) of the study population similar to Pehlivanoglu et al 23%.[3]followed by ischemic heart disease in 6(11.3%), hypertension in 7 (13.2%) patients. Other Co morbidities included Rheumatoid Arthritis in 2 patients, Chronic kidney disease in 3 patients, Scleroderma in 1patient and Parkinson's disease in 1 patient.

In our study most commonly observed symptoms were headache and fever in 51 (96.2%), cough in 30(60%), loss of appetite in 50 (94.3%) while 44 (83%) patients had seizure at presentation (Table no.1) comparable to other studies.[3,17,18]

In our study brain parenchymal involvement was seen in all patients while pulmonary involvement was seen in 45.3% patients and 11.3% patients had concomitant military TB. This was similar to that reported by Patel et al[14](46%) and 16% observed by Kaur et al[19].(133,130) Spine involment was seen in 8(15%)patients similar to salekeen et al 11.5%.[20]

Meningeal enhancement was seen in all patients followed by tuberculomas seen in 87% patients(Figure no.2). Radiological manifestations were more pronounced in our study as compared to other studies[13,19].

In our cohort, 23 patients required neurosurgical intervention in the form of Ventriculoperitoneal VP shunt in 22 and craniotomy in 1 patient. Very few studies in literature have reported use of VP shunt in adults. Salekeen et al observed that 15.4% TBM patients required VP shunt[20] while Lamprecht et al reported shunting in 65(29.9%) patients of childhood tuberculous meningitis and hydrocephalus[21].

CSF study was done in 46 (86.8%) patients as shown in Figure no.3. Mean value of ADA was found to be 12.3728 IU/L while mean values of other parameters of CSF analysis observed were Protein 422.54mg/dl, Glucose 36.52mg/dl, WBC 128.08cells/µL, Lymphocytes 74.07%, Neutrophil 19.15%, Monocytes 6.39%, Eosinophils 0.15% similar findings observed by Jingya Zhang et al study of TBM in non HIV patients[7].(9) Many studies has reported different findings[20,22,23].

Table no.2 shows analysis of CSF microbiology of 53 patients out of which 34 had microbiological proof of TB with one or more tests. AFB smear was positive in 7 patients, TB MGIT culture was positive in 28 patients. GeneXpert detected mycobacterium tuberculosis in 22 patients, 3 being rifampicin sensitive and 19 being rifampicin resistant. Jingya Zhang et al[7] **(9) and** R. S. Solomons et al[23] reported similar findings while Nguyen Thi Quynh Nhu et al[24] and Harsimran Kaur et al[19] reported higher findings.

Studies on the drug resistance of TBM are relatively rare. From the data available, the drug resistance pattern for TBM was obtained from four countries: Thailand, Egypt, Vietnam and South Africa. Information gathered from previous studies found that the average incidence of TBM that was resistant to any drug was approximately 21.5% (with a range of 12-31%). MDR-TBM was found in 2.2 to 8.6% of cases, with an average of approximately 3.3%. The incidence of MDR-TBM was up to 18% in paediatric cases, with a mortality rate of 100%.[25]

In our study high rates of drug resistant TBM was observed (43%) as shown in Figure no.4. This is comparatively higher compared to other studies which have reported drug resistance rates between 1-11%. This finding in our study could be attributed to our hospital being a tertiary referral centre in Mumbai which is a drug resistance hot-spot.

In our cohort, at the time of study analysis, 11 patients had died and 42 patients were still on treatment out of which 32.2% were treated with 1st line, 47.2% with 2nd line and 22.6% were treated with both line of treatment.

Of the 53 patients, 23 required neurosurgical intervention. 1 patient underwent craniotomy and 22 required ventriculoperitoneal (VP) shunt insertion.

Outcome was interpreted with MODIFIED RANKIN SCALE (MRS) where 11(20.8%) patients died of which 5 were drug resistant cases, 1 was sensitive TB and 5 were probable TBM. Higher mortality rates of 64.5% by Verdon et al[26]. and 43.6%. by Kaur et al were reported which could be explained by high number of sick patients who presented in the later stage of the disease[19].

While comparing Drug Resistant, Drug Sensitive and probable TBM patients, all features were comparable except increased incidence of past history of TB and presence of miliary TB in the drug resistant group. With regard to clinical features, there was increased confusion and weight loss among drug resistant TB patients. MRI findings showed increased parietal lobe involvement while CSF showed increased neutrophils among drug resistant TB patients.

Very few studies have compared drug sensitive and resistant TBM cases. Of these, Zhang et al reported significant extra meningeal involvement in resistant cases. Vomiting and disability was more commonly reported in resistant cases. No difference was observed between the two groups based on laboratory parameters[7].

Limitations

All patients were not followed up till treatment completion and most of the patients were referred to other centre, hence there was a referral bias and the study population does not represent the true population.

CONCLUSION

As TBM continues to be a serious problem for physicians to make an early diagnosis and to reduce the serious consequences of delaying treatment understanding the characteristics of TBM is very important. Long standing history of headache and fever, microbiological evidence along with biochemical analysis of CSF may should be considered. GeneXpert is an essential tool for early diagnosis of drug resistance in TBM. As involvement of other sites is frequently seen screening of other sites are important. Surgical intervention often forms an important component in management of TBM.

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