

**A STUDY ON THE CLINICAL FEATURES AND COMPLICATIONS OF TUBERCULOUS MENINGITIS IN A TERTIARY CARE CENTRE OF SOUTHERN INDIA**Rajashekar H. K<sup>1</sup>, Halesha B. R<sup>2</sup>, Chennaveerappa P. K<sup>3</sup>, Jayashree Nagaral<sup>4</sup>, Vivek Patnam Dinakar<sup>5</sup>**HOW TO CITE THIS ARTICLE:**

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**ABSTRACT: OBJECTIVE:** The study was carried out to describe the current epidemiology, clinical features, complications and outcomes in patients with tuberculous meningitis (TB Meningitis) in a tertiary care hospital of southern India. **SETTING:** Sri Chamarajendra District Hospital which is attached to Hassan Institute of Medical Sciences, Hassan, Karnataka, India. **STUDY DESIGN:** A record-based retrospective descriptive study. **MATERIALS AND METHODS:** Seventy cases of confirmed cases of tuberculous meningitis were studied between January 2011 and December 2013. The diagnosis of TB Meningitis was based on clinical and laboratory features. The data on the demographic factors, clinical features, complications, details of treatment and the outcome of these patients were recorded and analyzed. **RESULTS:** The mean age of the patients was 39.27 +/- 7.8 years with slight male predominance 39 (55.7%). Most common presenting features were fever (92.8%), altered sensorium (80%), and neck stiffness (77.2%). Among CNS (Central Nervous System) signs 63(90%) had signs of meningeal irritation, 21(30%) had cranial nerve palsies and 13 (18.57%) presented with Hemiplegia. 48(68.5%) patients presented in MRC (Medical Research Council) stage 2. The study revealed overall mortality of 11.42%, 38(54.28%) patients recovered completely without any residual deficits and 24(34.30%) patients had residual neurological sequelae. **CONCLUSIONS:** Tubercular meningitis is a serious central nervous system infection associated with significant mortality and high morbidity among survivors. The only way to reduce mortality and morbidity is by early diagnosis, timely recognition of complications and institution of appropriate treatment strategies.

**KEYWORDS:** Anti tubercular drugs, Hydrocephalus, Morbidity, Tuberculoma, Tuberculous Meningitis.

**INTRODUCTION:** Tuberculous meningitis (TB Meningitis) is a debilitating form of CNS tuberculosis with a high morbidity and mortality in spite of treatment. It is the most dangerous form of extra-pulmonary tuberculosis.

Though India is the second-most populous country in the world one fourth of the global incident tuberculosis (TB) cases occur in India annually. In 2012, out of the estimated global annual incidence of 8.6 million cases, 2.3 million were estimated to have occurred in India.

TB Meningitis is characterized by a slowly progressing granulomatous inflammation of the basal meninges. This inflammatory reaction can lead to a number of complications such as hydrocephalus, cerebral vascular infarction, cranial nerve palsy and if untreated, death.

Rapid diagnosis and initiation of treatment is necessary to reduce high mortality and severe sequelae associated with the disease.

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Diagnosis of TB Meningitis can be difficult as the symptoms are unspecific and mimic those of meningitis caused by other microbiological agents or other cerebrovascular events.

**MATERIALS AND METHODS:** This record-based, retrospective, descriptive study was carried out at Sri Chamarajendra District Hospital which is attached to Hassan Institute of Medical Sciences, Hassan, Karnataka, India. This institute is a referral government hospital in southern Karnataka, India catering to the patients hailing from Hassan, Madikeri and Chikkamagalur districts.

Seventy confirmed cases of TB Meningitis between January 2011 and December 2013 were retrospectively studied. In the study protocol, all confirmed cases of TB Meningitis, above the age of 12 years of both sex and informed consent were included.

The criteria for exclusion were age younger than 12 years, patients with CNS pathologies which can mimic TB Meningitis like Bacterial Meningitis, Viral Encephalitis, Subarachnoid Hemorrhage, Intra-Cranial Bleed, Cerebral Malaria, Stroke or Epilepsy.

Patients' hospital records were evaluated for clinical features, chest radiography, Montoux test, sputum smear for Acid Fast Bacilli (AFB), routine investigations, CSF (Cerebro-Spinal Fluid) studies, CT (Computerized Tomography) scan and MRI (Magnetic Resonance Imaging) scan of the head. On the basis of clinical presentation, patients of TB Meningitis were classified into 3 clinical stages according to the British MRC system.

All patients had been treated with conventional treatment according to the RNTCP (Revised National Tuberculosis Control Programme) Guidelines. Steroids were used in all of the patients.

The data on clinical features, laboratory findings and neuro-imaging reports were analyzed by SPSS software ver. 10. Clinical outcome of the patients studied were categorized as Complete Recovery, Recovery with Residual Neurologic Deficits (sequelae) and Death.

**RESULTS:** Of the 70 cases of TB meningitis studied, 39 (55.75%) were male and 31 (44.3%) were female. The mean age of the study population was 39.27 +/- 7.8 years with a range from 12 to 78 years (Median 37.5 years).

<b>Gender-Distribution of cases</b>		
<b>Gender</b>	<b>No. of cases</b>	<b>% of cases</b>
Male	39	55.70%
Female	31	44.30%
<b>Total</b>	<b>70</b>	<b>100%</b>
<b>Concurrent HIV(Human Immunodeficiency Virus) Infection</b>		
<b>HIV Status</b>	<b>No. of cases</b>	<b>% of cases</b>
HIV Positive	13	18.50%
HIV Negative	57	81.50%
<b>Pre-Existing Co-Morbid Disease or Clinical Condition</b>		
<b>Disease</b>	<b>No. of cases</b>	<b>% of cases</b>
Diabetes Mellitus	9	12.85%
Alcohol Abuse	8	11.42%
Immune-Suppressive therapy	3	4.28%
Acute Myeloid Leukemia	1	1.43%

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Systemic Lupus Erythematosus	1	1.43%
Chronic Kidney Disease	3	4.28%
<b>Total</b>	<b>25</b>	<b>35.71%</b>
<b>Co-existing Extra-Cerebral Tubercular Manifestations</b>		
<b>Manifestations</b>	<b>No. of cases</b>	<b>% of cases</b>
Pulmonary Tuberculosis	15	21.43%
Disseminated Tuberculosis	4	5.72%
Abdominal Tuberculosis	3	4.28%
Lymph Node Tuberculosis	3	4.28%
Spinal Tuberculosis	1	1.43%
<b>Total</b>	<b>26</b>	<b>37.20%</b>

**Table 1: Demographic Features in TB Meningitis**

16 patients (22.8%) gave a past history of tuberculosis. 21 patients (30%) reported a contact with tuberculous patient. 26 patients (37.2%) were found to have tuberculous infection affecting other organs at presentation. Of which pulmonary tuberculosis was found to be the most common association (21.43%), other types being disseminated tuberculosis (5.72%), abdominal tuberculosis (4.28%), lymph node tuberculosis (4.28%) and spinal tuberculosis (1.43%). Co-morbid diseases associated with tuberculosis are shown in table/fig 1.

<b>Presenting Symptoms in TB Meningitis</b>		
<b>Symptoms</b>	<b>No. of cases</b>	<b>Percentage</b>
Fever	65	92.80%
Neck Stiffness	54	77.20%
Headache	46	65.70%
Vomiting	28	40.00%
Altered level of consciousness	56	80.00%
Weight Loss	21	30.00%
Focal Weakness	16	22.80%
Seizures	11	15.70%
Behavioral Changes	12	17.20%
Photophobia	3	4.30%
<b>Objective Clinical Signs in TB Meningitis</b>		
<b>Objective Signs</b>	<b>No. of cases</b>	<b>Percentage</b>
Signs of Meningeal Irritation	63	90.00%
Cranial Nerve Paralyses	21	30.00%
Papilledema	15	21.40%
Hemiplegia/Monoplegia	13	18.70%
Choroidal Tuberculosis	3	4.3%

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<b>MRC (Medical Research Council) Staging of TB Meningitis</b>		
<b>MRC Stage</b>	<b>No. of cases</b>	<b>% of cases</b>
Stage 1	14	20.00%
Stage 2	48	68.50%
Stage 3	08	11.50%
<b>Total</b>	<b>70</b>	<b>100%</b>

**Table 2: Clinical Features in TB Meningitis**

Symptoms and signs at admission are summarized in the table/fig 2. Fever was the most frequent symptom which was experienced by 65 patients (92.8%), followed by altered level of consciousness in 56 (80%) cases and neck stiffness in 54 (77.2%) cases. (Table/fig 2). Objective clinical signs elicited by clinical examination are presented in table/fig 2. The mean GCS (Glasgow Coma Scale) score at presentation was found to be 12.5+/- 2.6.

Chest radiograph revealed pulmonary infiltrates in 8 patients, miliary pattern in 2 patients and pleural effusion in 3 patients and cavity in 2 patients.

<b>CSF (Cerebro-Spinal Fluid) Analysis</b>		
<b>CSF Analysis Findings</b>	<b>No. of Cases</b>	<b>Percentage</b>
Raised proteins	70	100%
Low glucose	57	81.42%
Lymphocytic pleocytosis	65	92.80%
Neutrophilic pleocytosis	5	15.00%
AFB Positivity	3	4.28%
<b>Neuro-Imaging Findings in TB Meningitis by CT (Computerized Tomography)</b>		
<b>Neuro-Imaging Findings</b>	<b>CT Detection Rate</b>	<b>Percentage</b>
Meningeal enhancement	21	40.30%
Tuberculoma	4	7.69%
Hydrocephalus	12	23.0%
Cerebral Infarct	4	7.90%
Cerebral Edema	5	27.8%
Encephalomyelitis	1	5.5%
Nil Pathology	20	38.46%
<b>Total</b>	<b>52/70</b>	<b>74.29%</b>
<b>Neuro-Imaging Findings in TB Meningitis by MRI (Magnetic Resonance Imaging)</b>		
<b>Neuro-Imaging Findings</b>	<b>MRI Detection Rate</b>	<b>Percentage</b>
Meningeal enhancement	11	61.20%
Tuberculoma	6	33.30%
Hydrocephalus	6	50.90%
Cerebral Infarct	4	21.205
Cerebral Edema	7	38.9%
Encephalomyelitis	1	5.50%
Nil Pathology	8	44.40%
<b>Total</b>	<b>18/70</b>	<b>25.71%</b>

**Table 3: Laboratory and Neuro-Imaging Features in TB Meningitis**

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CT and MRI neuro-imaging findings are summarized in table/fig. 3. 19 patients (27.15%) developed hydrocephalus, out of which 13 (18.5%) were of the communicating type, while 6 (8.6%) were of the obstructive type. Among these patients of hydrocephalus, Ventriculo-peritoneal shunt had to be placed in 12 cases and the rest were managed conservatively.

Duration of hospital stay ranged from 9 to 50 days with a mean of 20.08 +/- 6 days.

Clinical Outcome	No. of cases	% of cases
Complete Recovery	38	54.28%
Sequelae (Residual Neurologic Deficits)	24	34.30%
Death	8	11.42%

**Table 4: Outcomes of patients with TB Meningitis**

At the end of standard duration of treatment, 38 patients (54.28%) recovered completely without any residual neurologic deficits, whereas, 24 patients (34.30%) recovered with residual neurologic deficits like Hemiplegia, cranial nerve palsy(s), seizures and 8 patients (11.42%) died due to complication(s).

**DISCUSSION:** Mean age of patients was 39.27 +/- 7.8 years which is similar compared to previous studies.<sup>1</sup> Slight male predominance in this study is comparable to other studies.<sup>2,3</sup>

Most of the patients presented in clinical stage 2 MRC, which is in accordance with most of the other studies.<sup>2,3</sup> Delayed presentation leads to increased morbidity and mortality. Fever was the most frequent subjective symptom present in 65 patients (92.8%), followed by altered level of consciousness in 56 patients (80%) and neck stiffness in 54 (77.2%) cases. Clinical diagnosis of TB meningitis is difficult as the clinical features are non-specific and widely variable, and is often diagnosed when brain damage has already occurred.<sup>4-6</sup>

The clinical triad of meningitis viz. fever (adults – 60 -95 %; Children – 67%), headache (adults – 50-80 %; children – 25%) and signs of meningismus (adults – 40-80 %; children – 98%) – may NOT be present in all the patients.<sup>5</sup> Altered mental status is a more common presenting feature in children as compared to adults.<sup>6</sup> In the elderly, signs of meningismus may be absent and seizures occurs more commonly.<sup>7</sup> Patients with HIV co-infection may less commonly have fever, headache and meningismus, and they are more likely to present with altered mental status.<sup>8,9</sup>

CSF Pleocytosis with predominant lymphocytosis, increased protein and reduced sugar was found in >92.8%. However, 5 patients were found to have Neutrophilic pleocytosis. AFB smear was found positive in only 3 patients out of the total studied, which correlates well with other similar studies.<sup>2,3</sup> Evidence shows that atypical findings in CSF do not rule out tuberculous meningitis.<sup>1</sup> Acellular CSF has been reported in the elderly and in patients with HIV co-infection.<sup>4, 6, 10, 11</sup>

Bacteriological diagnosis by demonstration of acid-fast bacilli of Mycobacterium tuberculosis by Zeihl-Neelson stain (Sensitivity = 25%) and bacterial culture (Sensitivity = 18-83%) is highly specific (100%).<sup>6</sup> Tests to detect Mycobacterium tuberculosis specific antibodies and antigen in CSF of patients with TB meningitis are rapid and less expensive. But these techniques are limited by the inability to differentiate acute infection from previous infection and by problems with cross-reactivity, in addition to variable and often poor sensitivity and specificity.<sup>10</sup>

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Most common Neuro-imaging finding in this study is meningeal enhancement which is comparable to other studies.<sup>12</sup> A recent study found that MRI is superior to CT in identifying basal meningeal enhancement as well as infarcts. In the same study, hydrocephalus was detected equally by MRI and CT scans.<sup>13</sup> In conclusion, MR scans should be considered as the primary choice for Neuro-radiological imaging in the initial diagnostic phase in a high-resource setting.

Cochrane systematic review recommends routine use of corticosteroids in HIV-negative patients with TB meningitis to reduce the incidence of death and disabling neurological deficits among survivors.<sup>14-17</sup> In accordance, all patients in this study were treated with corticosteroids.

Sl. No	Year of Study	Author(s)	Total No. of Cases	Mortality Rate
01.	2014 – PRESENT STUDY	Rajashekar HK	70	11.42%
02.	2013	Salakeen S <sup>12</sup>	52	21.10%
03.	2012	Iype T <sup>20</sup>	98	27.00%
04.	2012	Shaikh MA <sup>21</sup>	50	6.00%
05.	2011	Christensen A H <sup>22</sup>	50	19.00%
06.	2008	Roca B <sup>23</sup>	29	41.00%
07.	2004	Thwaites <sup>15</sup>	274	36.00%

Table 5: Comparison of mortality in different studies

This study reveals an overall mortality of 11.42%. The cause of death was hydrocephalus and/or brain damage in all these patients that met with death. Whereas, the mortality as revealed by other studies range from 6.9% to 77% of patients studied in each of them.<sup>7,18,19</sup> (Table 5.). Higher mortality rate in other studies may be due to extensive disease (Stage 3 MCR), poor GCS status, MDR (Multi-Drug Resistant) or XDR (Extensively-Drug Resistant) strains of *M. tuberculosis* infection and delayed presentations.

At the end of standard duration of treatment, 38 patients (54.28%) had complete recovery without residual neurological deficits; 24 patients (34.2%) recovered with residual neurological deficit(s) including limb weakness, cranial nerve palsy(s) and seizures. Similar observations were made by few previous studies quoted.<sup>12</sup>

HIV co-infection does not alter the neurologic features of tuberculous meningitis but dramatically decreases the survival rate, although the incidence of severe disability in HIV-infected survivors may be equivalent or less than that in HIV-negative patients.<sup>24</sup>

**CONCLUSIONS:** TB Meningitis is a serious CNS infection associated with significant mortality and high morbidity among the survivors of the disease. Most factors found to correlate with poor outcome can be directly traced to the stage of the disease at the time of diagnosis.

The single most important strategy to reduce mortality and morbidity is probably early diagnosis, timely recognition of complications and institution of appropriate and prompt treatment modalities. However still, the most challenging aspect is the certainty of early diagnosis which is further hampered by slow and insensitive diagnostic methods. The other emerging yet dreaded challenge is the treatment of MDR-TB and XDR-TB cases.

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