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A PROSPECTIVE STUDY ON CLINICAL PROFILE AND OUTCOME OF PATIENTS WITH TUBERCULOUS MENINGITIS AT A TERTIARY CARE CENTRE IN MAHARASHTRA

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ABSTRACT

BACKGROUND: Tuberculous meningitis (TBM) is one of the most fatal forms of tuberculosis, early diagnosis and treatment of which can reduce morbidity and mortality. This study was undertaken to achieve data regarding clinical profile and outcome of patients from western India as epidemiological data is lacking from this region.

METHODS: This prospective observational study was conducted on 136 patients admitted in medical ward and critical care unit of a tertiary care hospital in Maharashtra over 18 months. Clinical, biochemical, radiological and microbiological evaluation was done. Data was analyzed using SPSS 22 version software and p value of <0.05 as significant.

RESULTS: The mean age of cases was 35.2 ± 14.69 years, majority from age group of 18 - 40 years. Out of 136 cases, 62 (45.6%) were males and 74 (54.4%) females. Commonest clinical features were fever and headache, followed by altered sensorium and seizure. Symptoms were mostly of acute onset (<14 days). 42 cases (30.9%) were associated with present or past pulmonary tuberculosis and 34 (25%) with retroviral disease. 7 cases (5.2%) had hemiparesis and 3 (2.2%) had ophthalmoplegia. Mean ESR was 56.59 ± 22.87. CSF showed lymphocytosis (mean 88.4 ± 18.09 %), low glucose percentage (mean 39.57 ± 0.2 %) and high protein (mean 146.02 ± 106.62 mg/dl). 117 cases (86%) showed positive neuroimaging. Outcome was poor in stage III disease.

CONCLUSION: Tuberculous meningitis usually presents as acute onset illness with fever, headache or altered sensorium. CSF Gene Xpert has low sensitivity as compared to neuroimaging. Advanced disease was associated with poor outcome.

KEYWORDS : tuberculous meningitis, clinical profile, biochemical, radiological, staging

BACKGROUND

Tuberculosis (TB) is one of the oldest diseases amongst humans and the largest cause of death by infections. It predominantly affects the lungs; however, other organs can be affected in about one-third of the cases. Central nervous system (CNS) accounts for ~5% of these extra-pulmonary cases. If properly and timely treated, it is curable in a good number of cases. If untreated, CNS tuberculosis can be uniformly fatal. India is the country with the highest burden of tuberculosis. World health organization (WHO) TB statistics (2016) for India estimated about 2.79 million cases of TB in India. It has been noted that global incidence of TB is increasing by 0.4% per annum. About 5-10 % of these develop CNS disease.[1]

The disease often presents subtly as headache and slight mental changes after a prodrome of weeks of low-grade fever, malaise, anorexia, and irritability. Although the presentation and duration of disease may vary greatly. If not recognized, tuberculous meningitis may evolve acutely with severe headache, confusion, lethargy, altered sensorium, and neck rigidity. Typically, the disease evolves over 1–2 weeks. Because meningeal involvement is more pronounced at the base of the brain, cranial nerve palsies, esp. ocular cranial nerves, are frequently seen; and the involvement of cerebral arteries may produce focal ischemia. The progression of the disease is towards coma, with hydrocephalus and intracranial hypertension; thereby leading to death. [3]

Current major challenges to successful management of patients with TBM are: -

1) Difficulty in early diagnosis due to vague and varied clinical presentations and low sensitivity diagnostic laboratory parameters
2) Emerging strains of drug resistant TBM
3) Management of complications such as vasculitic infarcts, hydrocephalus, tuberculomas etc.

TBM is a common type of meningitis in our setting. There is no adequate data regarding clinical profile or outcome of TBM patient from this region. So, we undertook this study.

METHODS

This is prospective observational study conducted on 136 patients admitted in medical ward and medical ICU of tertiary care of hospital (Grant Government Medical College and Sir JJ Group of Hospitals). All consecutive, diagnosed cases of Tuberculous meningitis admitted in medicine wards and Medicine ICU were enrolled in this study. The study period was from January 2018 to July 2019. IEC clearance was taken from the institutional ethics committee at JJ Hospital.

INCLUSION CRITERIA: (A) Clinical findings: Fever, headache and vomiting, altered sensorium, focal deficit of any duration (B) cerebrospinal fluid (CSF) showing: (i) pleocytosis (>20 cells, predominantly lymphocytes (>60%)), (ii) proteins > 100 mg%, (iii) sugar < 60% of corresponding blood sugar (C) CT or MRI scanning brain showing one or more of (i) basal or sylvian exudates (ii) hydrocephalus (iii) infarcts (iv) Gyral enhancement (D) radiology or microbiology or histopathology evidence of extraneural tuberculosis Cases were classified as: *1)* Definitive TB meningitis [4]: (A) + bacterial isolation from CSF by staining, culture or CB-NAAT 2) Highly probable TB meningitis [4]: (A) + (B) + (C) + (D) 3) Probable TB meningitis [4]: (A) + any 2 of (B), (C) or (D) 4) Possible TB meningitis [4]: A + any 1 of B, C or D

EXCLUSION CRITERIA: (1) Patients who do not give consent for the study (2) Patients </= 12 years of age (3) meningitis after trauma (4) Cases with spontaneous improvement without anti-tuberculous therapy (5) pyogenic organisms on CSF staining or culture (6) fungal growth evidenced by positive CSF Indian ink staining or CSF Culture Grading of the disease was done as[6]: Grade 1 – Glasgow coma scale (GCS) 15: without focal neurological deficit; Grade 2 – GCS 14-10: with or without focal neurological deficit; Grade 3 – GCS < 10:

with or without focal neurological deficit. BMRC Staging of disease [7] (done at the time of initiation of anti-tuberculous treatment): Stage 1: no definite neurological symptoms on admission or in the history before admission, with or without meningismus; Stage II: Signs of meningeal irritations with or without slight clouding of consciousness with focal neurological signs such as cranial nerve palsies or hemiparesis; Stage III: severe clouding of consciousness or delirium, convulsions and serious neurological signs such as hemiplegia, paraplegia, involuntary movements

Outcome was assessed as: Morbidity – patients with any residual focal neurological deficit at the end of one month from initiation of anti-tuberculous treatment; Mortality – death within one month of initiation of anti-tuberculous treatment; Good response – patient having neither morbidity nor mortality

After detailed history and physical examination, each case underwent basic investigations like CBC, LFT, RFT, FBS, PPBS, ECG, CHEST X RAY, SPUTUM FOR AFB; Neurological examination to assess the GCS and motor function; Fundoscopy; CSF examination for sugar, cells, proteins, gram staining and ZN staining; Special investigations like CSF ADA, CSF CB-NAAT, cryptococcal antigen, India ink preparation and culture for mycobacterium tuberculosis. CT or MRI scanning of brain were done to facilitate the diagnosis as per the need. Cases were followed up during their entire hospitalization course to assess the short term outcome. If the case was discharged, follow up was done after one month.

Statistical analysis: Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Continuous data was represented as mean and standard deviation. A p value of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

RESULTS:

Total 136 cases were studied. Median age was 34 years. It was slightly more common in females as compared to males. Commonest presenting complaints were fever, headache and altered sensorium. Median duration of illness before admission was 15 days. Past history of pulmonary tuberculosis was present in 42 (30.9%) cases, while present evidence of pulmonary tuberculosis was seen in chest X-ray of 23 (16.9%) cases, out of which 12 were sputum positive. 34 cases (25%) were associated with retroviral disease. Median ESR was 55.5. Hyponatremia (i.e. serum sodium 135mg/dl) was seen in 55 (40.4%) cases. CSF for Gene Xpert was positive in 19 cases (13.3%) out of which one case had Rif resistance. Mean CSF protein was 146, mean sugar was 39, mean TLC was 84.7 and mean ADA was 8.4 IU/L. CT brain was suggestive of CNS tuberculosis in 91 (66.9%) cases. On follow up at the end of one month of treatment, 50 cases (36.8%) were found to be asymptomatic and 70 cases (51.5%) had some morbidity. Among the 70 cases that had morbidity at the end of one month, the commonest symptoms were headache i.e. 18 cases (25.7%); followed by motor weakness in the form of right/left hemiparesis i.e. 13 cases (18.6%) and altered sensorium in 9 cases (12.9%). Other morbidities were cognitive impairment, persistent fever, diplopia, other visual disturbances and seizure. 3 patients also developed hepatotoxicity secondary to anti-tuberculous treatment. Mortality was found in 16 cases (11.8%) within one month. Multivariate analysis showed presence of altered sensorium, CSF TLC > 150/mm and high CSF protein (>100mg/dl) were significant risk factors for mortality in TBM patients.

Table 1: Demographic distribution of cases (n=136)

Attribute:		No of cases (Percentage (%));
Age group (in years)	< 18	15 (11.02%)
	18 -30	39 (28.67%)
	31- 40	39 (28.67%)
	41 -50	21 (15.44%)
	51-60	14 (10.29%)
	>60	08 (05.88%)
Sex	Male	62 (45.55%)
	Female	74 (54.54%)

Table 2: Frequency of clinical symptoms, duration, diagnostic category, grading and staging of cases (n=136)

Attribute		No of cases (Percentage (%))*
Clinical feature	Headache	86 (63.3%)
	Fever	100 (73.52%)
	Vomiting	28(20.58%)
	Seizure	24 (17.56%)
	Altered sensorium	41 (30.14%)
	Others #	29 (21.32%)
Motor deficit	Hemiparesis	7 (5.14%)
	Ophthalmoplegia	3 (2.2%)
Duration of illness before admission (Days)	< 14	54 (39.70%)
	14-28	31 (22.79%)
	>28	51 (37.50%)
Diagnostic category	Definitive	19 (13.97%)
	Probable	81 (59.55%)
	Highly probable	9 (6.61%)
	Possible	27 (19.5%)
Stage	Stage I	26 (19.11%)
	Stage II	76 (55.58%)
	Stage III	34 (25.31%)
Grade	Grade I	97 (71.32%)
	Grade II	23 (16.91%)
	Grade III	16 (11.76%)

#Others include – decrease vision, forgetfulness, unilateral weakness, cough, diplopia.

*Most of the cases have more than one clinical feature so the total percentage is more than 100.

Table 3. CSF Analysis and radiological findings among enrolled cases (n=136)

CSF examination	No of cases (Percentage (%))	
Appearance	Clear	102 (75%)
	Hazy	34 (25%)
ZN stain	Negative	136 (100%)
CSF gene expert	Negative	117 (86.02%)
	Positive (RIF resistant)	1 (0.07%)
	Positive (RIF sensitive)	18 (13.23%)
	Mean	**Median (range)**
TLC (/mm3)	84.69 ±125.28	25 (0-562)
Lymphocyte (%)	88.40 ± 18.09	100 (0-100)
Sugar (mg/dl)	46.88 ± 23.52	41 (10-104)
RBS at LP (mg/dl)	117.85 ± 22.52	114 (80-232)
Sugar (%)	39.57 ±0.20	36 (1-91)
Protein (mg/dl)	146.02 ± 106.62	123 (22- 634)
*ADA (IU/L)	8.40 ± 7.74	4.90 (0.40-44)
CT brain		**No of cases (percentage %)**
	Normal	45 (33.0%)
	Tuberculomas	50 (36.76%)
	Hydrocephalous	29 (21.32%)
	Vasculitis	1 (0.7%)
	Gyral enhancement	11 (8.08%)

Table 4. Outcomes of cases at the end of one month (n=136)

Outcome	No of cases (Percentage (%))
Asymptomatic	50 (36.76%)
Morbid	70 (51.47%)
Mortality	16 (11.76%)

Table 5. Multivariate analysis of mortality

Variables	*Corelation value*	*Standard Error*	*P-value*	*95% confidence interval*
Age (>35years)	0.035	0.058	0.547	-0.080-0.150
Gender (Male)	0.029	0.054	0.598	-0.078-0.136
Seizure	0.029	0.073	0.692	-0.115-0.172
ALTERED SENSORIUM at presentation	0.237	0.060	0.001	0.119-0.356
Duration of illness before admission (<14 days)	0.003	0.056	0.963	-0.109-0.114
HIV positive	-0.025	0.067	0.704	-0.157-0.107
CSF gene expert (positive)	0.110	0.080	0.171	-0.048-0.269
CSF TLC (>150/mm^3)	-0.132	0.065	0.045	-0.260-(-0.003)
CSF PROTEIN (>100mg/dl)	0.112	0.059	0.047	-0.004-0.229
CSF SUGAR (<30%)	-0.091	0.066	0.170	-0.222-0.040

DISCUSSION:

There was slight female preponderance seen in our study (consistent with studies by Showkat et al[4] and Saleem et al[3]). This may be in accordance with the fact that although worldwide, there is male preponderance for pulmonary tuberculosis, more severe forms are common in females owing to poor education and delayed healthcare access to women in developing countries like India. The study population was divided into 6 groups as per age, with highest age wise distribution in age group 18-30 and 31-40 years, with mean age 35.2 $\pm$ 14.69 years. Similar result was seen with study by Showkat et al[4] where mean age was 36.26 $\pm$ 17.08 years. This could be due to the fact that young age group is exposed to more outdoor activities and thus, greater exposure to infection. Also, the delayed healthcare access in elderly may lead to cases not being reported. Headache (in 63% cases), fever (in 73% cases) and vomiting (in 21%) were the commonest symptoms at presentation, findings consistent with study by Saleem et al. [3] and Showkat et al. [4] Other symptoms seen were seizure, altered sensorium, decreased vision or diplopia, forgetfulness and unilateral weakness. The symptoms were usually of acute duration (2 weeks) in our study, a finding similar to study by Showkat et al. [4]The results were discordant to the study by Saleem et al.[3] where duration of symptoms was more than 2 weeks, with 40 (53%) cases from 76 cases enrolled having duration more than 4 weeks. This greater duration of symptoms can be attributed to difficult access to specialised medical centres in the region where study was conducted (i.e. Kashmir valley). The number of cases associated with pulmonary tuberculosis was quite high in our study as compared to study by Saleem et al. [3], where only 6 (7.89%) out of total 76 cases were found to have history of pulmonary tuberculosis and 8 cases (10.52%) had family history of pulmonary tuberculosis. On the basis of Glasgow coma scale, cases were categorised into grades 1-3 on presentation. Maximum cases presented with grade 1 of disease. The mean Glasgow coma scale score was 13.4 $\pm$ 2.66. Cases were divided into stages on the basis of clinical features, at the time of initiation of treatment. Maximum cases were found in the stage II of disease. In study by Saleem et al.[3] also, maximum cases were in stage II, followed by stage III. there are a significant number of cases in our study who were already in stages II/III by the time treatment was initiated. Delayed seeking of medical care could be one reason for this. Other causes can be delayed recognition of symptoms, poor sensitivity of available tests or unavailability of radio diagnosis facilities in remote areas. The disease also has a rapid course in some patients. Mean ESR was found elevated in our study i.e. 56.59 $\pm$ 22.87. ESR was found high in study by Showkat et al.[4] i.e. 25.04 $\pm$ 11.93. Tuberculosis is a destructive disease as well as a chronic disease and therefore, fibrinogen and gamma globulin levels increase, which will increase rouleaux formation and thereby ESR [8] [9]. Hyponatremia was found in 55 cases (40.4%) of 136 cases in our study. It may be due to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, cerebral salt wasting syndrome (CSWS), excessive fluid administration in patients with impaired thirst, diuretic therapy such as mannitol, and treatment of transient/permanent diabetes insipidus. [10] [11] [12]

Analysis of CSF abnormalities, to a great deal, facilitates the diagnosis and influences the initial therapy. In our study, the mean CSF TLC was 84.69 $\pm$ 125.28, which was much lower as compared to other studies. The difference could be due to larger sample size in our study. In early phase, CSF exhibits an increased number of neutrophils, however, the picture turns lymphocytic in the tissue repair stage. [2] Mean CSF sugar was 46.88 $\pm$ 23.52, higher as compared to other studies. The mean CSF protein was 146.02 $\pm$ 106.62 which was lower than other studies. The mean ADA level in our study was 8.40 $\pm$ 7.74, which was also lower as compared to other studies. Hence, ADA level was found to be a less sensitive indicator for tuberculous meningitis.

All cases were started on anti-tuberculous treatment and were followed up after one month. Outcomes were matched against the stage of disease.

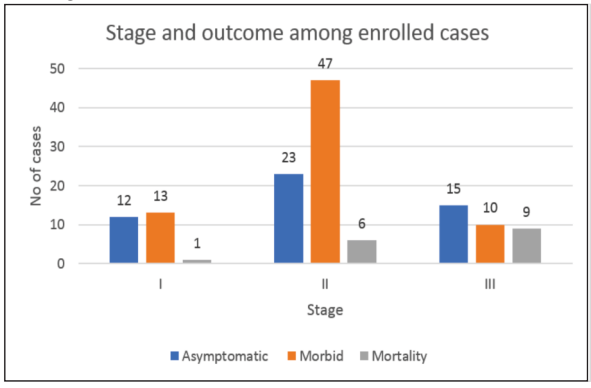

Fig. 1 Stage and outcome among enrolled cases

Mortality was high among cases in stage III (26.47%). At the end of one month, a significant number of cases were still symptomatic (50% on stage I and 61.4% of stage II). A total of 50 cases from 136 cases enrolled, were asymptomatic at the end of one month. A total of 16 cases (4 confirmed, 8 probable and 4 highly probable cases) died in our study due to the disease, within one month. Amongst the deaths, the mean age was 44.81 years (consistent with study by Harsimran Kaur et al. [5]); there were 9 males and 7 females; mean duration of illness before presentation was 17.44 days; mean Glasgow coma scale score was 9.25.

LIMITATIONS OF THE STUDY

1) The study was carried out at a single centre, which is not sufficient to represent the characteristics of entire region.
2) TB is a chronic disease with an insidious start, making it difficult for patients to remember exactly when the symptoms started. Thus, recall bias can be present.
3) Follow up time was one month. Longer follow up is needed to comment on permanent neurological sequalae or other complications of this disease.

4) In cases admitted with altered sensorium, history was noted as given by the relatives. Hence making it less reliable.

CONCLUSION

Tuberculous meningitis is mainly the disease of adults in this region, with slight female preponderance. It usually presents as acute onset illness and fever, headache, altered sensorium, vomiting and seizure are among the most common presenting complaints. Present or past pulmonary tuberculosis and retroviral disease are among the most common associated comorbidities. CSF Gene Xpert has got low sensitivity as compared to neuroimaging in diagnosis of tuberculous meningitis. Hyponatremia was commonly seen in TBM. Advanced disease (stage III) was associated with poor outcome.

Conflicts Of Interest

The authors have no conflict of interest.

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