Original Article

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Seizures, Hepatotoxicity and Advanced Disease Are the Greatest Predictors of Death in Tubercular Meningitis

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Abstract

The prevalence of Tuberculous meningitis is increasing in developing countries including in India. Many complications, long term sequelae and deaths are associated with tuberculous meningitis. Our aim is to access the complication in different stages of tuberculous meningitis and to identify the predictors of mortality. Method This prospective study was conducted in tertiary care hospital, Eastern India from (May2013- June 2016). Study included patients suffering from tuberculous meningitis proved by history, clinical examination, CSF study and radiological imaging. The patients were then classified according to different stages of tuberculous meningitis and observed for the complications including seizures and drug induced hepatitis and mortality differed between the three stages. All the patients were put on treatment and followed up. Result A total of 100 cases were enrolled in which 54 were males and 46 females with median age 29.2+11.15 years. 36%, 37% and 27% of patients presented in stage I, stage II and stage III respectively. 46% developed hydrocephalus, 29% had cranial nerve palsy, 24% had stroke, 23% had seizures, 17% developed tuberculoma, 13% had hypodensities suggestive of vasculities and basal exudates were seen in 33%. 17 patients were died during hospital stay and 83 patients were discharged. Conclusion Our study showed the disease is more prevalent in younger population equally affected males and female. The rate of central nervous system complication is high every complication contributes to morbidity and mortality but the greatest predictors are seizure, stroke, drug induced hepatitis and advanced stage of disease.

Keywords: Tubercular Meningitis; Seizures; Hepatotoxicity.

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Introduction

Developing countries like India has a huge global burden of tuberculosis. Data from USA showed that most of the tuberculosis cases occur in individuals from 5 countries: Mexico, the Philippines, India, Vietnam, and China [1]. The prevalence of tubercular meningitis (TBM)is a reflection of the prevalence of tuberculosis in the area. Around 10% of individuals who have tuberculosis develop central nervous system tuberculosis [2]. The epidemic of human immunodeficiency virus infection has increased the incidence of tuberculosis and tubercular meningitis in both developing and developed countries.

Tubercular meningitis is associated with acute complications, long term neurological sequelae, other co-morbidities and death. The estimated mortality due to tuberculous meningitis in India is 1.5 per 100,000 population [3].

Aims and Objectives

The aim of the study was to determine i) the distribution of cases of tubercular meningitis based on stages. Stage I, II and III; ii) the presence of complications in patients with tubercular meningitis;

iii) which complications differed between the three stages; and iv) to identify the predictors of death in patients with tubercular meningitis.

Materials and Methods

This was a prospective study conducted in a tertiary care teaching hospital in Eastern India. 100 consecutive patients of tuberculous meningitis admitted in the Medicine Ward over a period of three years (May 2013-June 2016) were included in this study. The patients were diagnosed on the basis of history, clinical features, biochemical, radiological and CSF examination results. During their hospital stay all the patients were examined, treatment started and assessed for complications.

A detailed history of the illness, symptoms suggestive of pulmonary and extra pulmonary site involvement, family history, contact history, prior history of tuberculosis and/oranti-tubercular therapy (ATT) was taken. The age and gender of the patients were noted, details of personal history including addiction and any co-morbidities were taken where possible.

A through clinical examination including general survey, CNS examination including GCS, signs of meningeal irritation, cranial nerve palsies, abnormal movement and papilledema, breath sounds and any abnormal sounds in respiratory system, ascites and hepatomegaly in abdominal examination. Clinically patients were assessed for complications like altered consciousness, seizures, cranial nerve palsy (CNP) and focal neurological deficit.

Diagnosis of TBM was made by history of fever, vomiting, headache, signs of meningeal irritation like neck stiffness, photophobia, CSF finding of raised protein, low glucose, lymphocytic pleocytosis, raised adenosine deaminase levels (ADA) and AFB positivity. The severity at presentation was assigned according to british Medical Research Council (BMRC) criteria stage I: fully conscious and rational without focal signs; stage II: lethargy, altered behaviour, meningism or minor focal signs; and stage III stupor, coma, or a severe focal neurological deficit [4].

Other necessary investigations like complete blood count, liver function test, urea, creatinine, electrolytes chest X-ray, CT scan head and fundoscopy were done in all patients.

Patients with deranged liver function test (LFT) also had blood testing for hepatitis A, E, C and D. Drug induced hepatitiswas diagnosed as alanine transaminase (ALT) 5 times the upper limit of normal (ULN) in those without symptoms and 3 times rise the ULN in symptomatic patient; in a patient receiving ATT with no apparent cause of deranged ALT and a normal ALT prior to the start of ATT.

The patients were put on ATT, those who developed complications were managed accordingly and discharged in stable condition. A follow up protocol was devised, the patients & there relatives were counselled about to continue treatment and periodic follow up.

SPSSv21 was used for statistical analysis of data. $p<0.05$ was considered significant

Results and Analysis

100 consecutive cases of TBM were enrolled in the study. There were 54 males and 46 female patients, with median age of 29.2±11.15 years and age range of 16-61 years. 36%, 37% and 27% of the patients presented in stage I, II and III respectively, which meant that a higher proportion of individuals presented in the more advanced stages of the disease namely stage II and III. 46% developed hydrocephalus, 29% had cranial nerve palsy, 24% had stroke and 23% had seizures. Drug induced hepatotoxicity developed in 17% of the individuals. Basal exudates was seen in 33%, dilated ventricles in 46%, hypodensities suggesting vasculitis in 13% and 17% had tuberculoma. 83% was discharged whereas 17% of the patients died in the hospital.

Univariate analysis showed that ALT, AST, prothrombin time (PT), INR and serum creatinine

Table 1: Showing different parameters between death and discharge

Parameter	Discharged	Death	P value
ALT	54.6±54.24	176.9±128.13	0.001
AST	50.34±37.63	120.7±88.4	0.005
PT	12.19±2.5	19.29±7.2	0.001
INR	1.1±0.19	1.71±0.66	0.002
Cr	1.10 ±0.43	2.05±1.08	0.002
Age	28.5 ±11.6	32.29±7.7	0.21

were significant predictors of death. Table 1 shows that the AST, ALT, INR and creatinine were all significantly higher in those who died compared to those who were discharged. However there was no statistically significant difference in age between the two groups.

Univariate analysis by pooled chi-square test showed that more patients in stage III died (52.9%) compared to stage II (41.2%) and stage I (5.9%); and more people in stage I was discharged (42.2%) compared to stage II (36.1%) and 21.7% with p value of 0.005. Univariate analysis by pooled chi-square test further showed that the following parameters were significantly higher in death compared to discharge: CNP (64.7% vs 21.7%; p 0.001), stroke (52.9% vs 18.1%; p 0.004), seizure (52.9% vs 9.6%; p 0.003) and hepatotoxicity (52/9% vs 9.6%; p0.001).

Multivariate Logistic Regression Model Predicting Outcome (Death vs. Discharge) in Tuberculous Meningitis showed that only seizure and hepatotoxicity was found as a significant predictor of death. Hepatotoxicity was associated with 9.58 times increased chances of death. OR – 9.05, 95% CI – 1.801-51.02, p=0.007. Seizure was associated with 10.31 times increased chances of death. OR – 10.306, 95% CI – 1.104-96.177, p=0.046.

Comparing individuals in the 3 stages it was found that there was no statistically significant differences in age, ALT, AST, PT and INR in the 3 stages but serum creatinine was statistically higher in stage III (compared to stage II to stage I (1.6±0.83, 1.2±0.69 and 1.03±0.39 respectively, p=0.001). Hydrocephalus and cranial nerve palsies were highest in stage II (33.3%, 55.6%). However there was higher incidence of strokes in stage III (55.6%) compared to stage II (25%), and no strokes in stage I. the p value was <0.001. Seizure was also highest in stage III (63%) compared to stage II (11.1%) and stage I (5.4%); p<0.001). Death was also significantly higher in stage III (33.3%) compared to stage II (19.4%) and stage I (2.7%); p 0.001.

Discussion

In our study TBM affected the young adults thereby causing death and disability in the most productive periods of their lives. TBM has a high complication rate with a large portion of patients dying (17%). The prevalence of complications likeseizures, strokes, cranial nerve palsy, hydrocephalus and hepatotoxicity is high and most of these complications individually are predictors of death. However the greatest predictor of death are hepatotoxicity and seizures. Stage III was also a predictor seizures and death. So it can be said that the biggest predictors of death are hepatotoxicity, seizures and stage III disease in our study. The possible causes of strokes are blockage of blood vessels by exudates, arteritis and vasculitis and the pro-thrombotic state of TBM.

In our study hydrocephalus was the most common neurological complication (46%) followed by CNP, strokes and seizures. In a study from New Zealand that incidence of hydrocephalus was 42% which is similar to our finding [5]. Stroke incidence in TBM is highly variable in many studies due to many factors like different diagnostic criteria for stroke, imaging modality and difficulty in diagnosing stroke in a comatosed patient.

It is interesting the hepatotoxicity and seizures were the biggest predictors of death. The mechanism by which hepatotoxicity can be associated with death is multi-pronged. One mechanism is death due to hepatic encephalopathy but probably that is not the main mechanism by which it predicts death. Hepatotoxocity could be a marker of underlying severity of the disease. In a study that tried to identify the predictors of hepatotoxicity in TBM it was seen that seizures and hypoalbuminemia were the greatest predictors of hepatotoxicity [6]. So it is no co-incidence that in our study both seizure and hepatotoxicity were greatest predictors of death along with stage III disease.

Seizure could contribute to hepatotoxicity due to the use of anti-epileptic agents which may have effects on the liver. Seizure is a manifestation of underlying problems that include but not limited to electrolyte imbalance, hypoglycaemia and strokes. The underlying problems can lead to increased mortality in seizures. Seizure associated complications like aspiration and trauma further contribute to death. In a study from Pakistan the predictors of death were old age; advanced stage of tuberculous meningitis, serum sodium <125 mmol/l, TLC>9000/μL development of hydrocephalus and use of mechanical ventilation as major predictors of mortality [7]. Our study did find advanced stage disease as a predictor of death but not age or hydrocephalus. This could be because of the fact that most of our patients were relatively young and the median age was quite low and therefore the role of age as a determining factor in outcome in minimized.

The high prevalence of stroke in our study and hypodensities of CT scan can be attributed to tuberculosis associated vasculities and arteritis. In a study from India, it was seen on autopsy thatthere wasextensive damage of cerebral vessels in TBM,

which was responsible for the presence of widespread infarctions. Microscopic infarctions in the brainstem and cerebellum were much more common than reported by radiological studies [8].

Conclusion

Our study found that TBM occurs mainly in the young adults with both men and women equally affected. The complication especially the CNS complication rate is high. Individually a number of factors cause contribute to death, but the greatest predictors are seizures, strokes and advanced stage disease.

References

1. Trends in tuberculosis—United States, 2012. Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep. 2013 Mar 22;62(11):201-5.
2. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: Estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 1999;282:677-86
3. Chakraborty AK. Estimating mortality from tuberculous meningitis in a community: Use of available epidemiological parmeters in the Indian context. Ind J Tub 2000;47:9-12.
4. BMRC (British Medical Research Council).
5. N.E. Anderson, et al. Neurological and systemic complications of tuberculous meningitis and its treatment at Auckland City Hospital, New Zealand. Journal of Clinical Neuroscience 2010;17:1114–1118.
6. Usha K Misra, et al. Predictors of Drug Induced Hepatotoxicity in Tuberculous Meningitis. Neuroinfect Dis 2014;5:2.
7. SirajusSalekeen, et al. Clinical course, complications and predictors of mortality in patients with tuberculousmeningitis—an experience of fifty two cases at Civil Hospital Karachi, Pakistan. JPMA 2013;63:563.
8. Chatterjee D, Radotra BD, et al. Vascular complications of tuberculous meningitis: An autopsy study. NeurolIndia [serial online] 2015;63:926932. [cited 2017 Feb 27].