Original Research

Factors Affecting Prognosis in Tuberculous Meningoencephalitis

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ABSTRACT

Introduction: Cases of tuberculosis is still highly prevalent in the world, including Indonesia.Tuberculous meningoencephalitis (TBME) is the most severe form of tuberculosis. This study aims to establish the factors affecting prognosis in TBME.
Objective: To Identify the clinical factors that affect the prognosis of tuberculous meningoencephalitis patients.
Material and Methods: This is cross-sectional study evaluating factors (clinical features, imaging, and treatment) affecting prognosis in TBME patients who underwent treatment in Siloam Hospitals Lippo Village. Univariate analyses was done, followed by bivariate analyses with logistic regression to compare factors between good (Glasgow outcome scale [GOS] 4-5) and poor (GOS 1-3) prognosis.
Results and Discussion : 64 patients were included. On univariate analysis, significant differences was found between Glasgow coma scale (GCS) scores (p=0.012), clinical features of meningeal irritation (p=0.004), findings of hydrocephalus (p=0.023) and vasculitis/infarction (p=0.020) on imaging, antibiotic use (p=0.013), and MRC grading (p=0.008). On logistic regression, 4 factors were found to be significant: headache (OR 5.398 95% CI 1.165-25.008, p=0.031), meningeal irritation (OR 0.146 95% CI 0.026-0.813, p=0.028), hydrocephalus (OR 0.167 95% CI 0.032-0.881, p=0.035), and antibiotic use (OR 0.155 95% CI 0.034-0.717, p=0.017).
Conclusion: Clinical manifestations of meningeal irritation and altered consciousness, imaging findings of hydrocephalus and vasculitis/infarction, and antibiotic usage is associated with poor prognosis, while presence of headache is associated with a better prognosis.

Keywords: meningitis; meningoencephalitis; tuberculosis; prognosis

INTRODUCTION

Tuberculosis (TB) constitutes a global issue, affecting more than 1.7 million people or 22% of the global population.[1] Based on data from the World Health Organization (WHO), there are more than 10 million new cases of TB in 2019, and 1.5 million deaths. The incidence of TB varies across nations, in which the majority of cases (44%) is found in Southeast Asia. Indonesia is the second-leading nation in terms of TB case numbers, accounting for 8.5% of the global TB case burden.[2]

Although TB primarily involves the lungs, *Mycobacterium tuberculosis* infection can present with a number of extrapulmonary manifestations, including those affecting the central nervous system (CNS). Tuberculous meningoencephalitis (TBME) is the most common CNS complication and most severe form of TB and occurs as a result of leptomeningeal and parenchymal inflammation by *M. tuberculosis* infection.[3,4] TBME has a high mortality rate, ranging from 55 to 75%,[5] and can result in severe neurological complications such as hydrocephalus and blindness.[6] Therefore, it is crucial to uncover the factors affecting prognosis in TBME, in hopes of improving and optimizing treatment.

MATERIAL AND METHODS

Sample population

The sample population in this study includes all patients with a diagnosis of tuberculous meningitis/ meningoencephalitis who was undergone treatment in the inpatient department of Siloam Hospitals Lippo Village in a five-year period (January 2017 to December 2022). Patients with incomplete data, as well as patients with a final diagnosis excluding TBME, are excluded from the sample.

Study design

This is a retrospective cross-sectional study evaluating the impact of factors towards prognosis in TBME patients. Data was collected in consecutive-retrospective fashion via the medical record. We collected information regarding demographics (sex, age), disease severity (as measured by the Medical Research Council [MRC] scale) (table 1),[7] clinical features (*Glasgow coma scale* [GCS] score at presentation, presence of fever, headache, nausea/vomiting, meningeal irritation, altered consciousness, seizure, focal neurological deficits), past medical history (*human immunodeficiency virus* [HIV] infection status, extra-CNS TB manifestations, history of past anti-tuberculosis drug [ATD] treatment), findings on head computed tomography (CT) or magnetic resonance imaging (MRI) (presence of tuberculoma, hydrocephalus, vasculitis/infarction), treatment (administration of glucocorticoids, non-tuberculous

antibiotics, antiepileptics, and antipyretics), as well as prognosis (as evaluated by the Glasgow outcome scale [GOS] at discharge).[8,9] This study has been approved by the research ethics committee of the Faculty of Medicine, Pelita Harapan University.

Table 1. Medical Research Council (MRC) grading for TBME severity.[7]

Grade	Criteria
I	Fully alert and oriented without focal neurological deficits
II	GCS 14-11, or 15 with focal neurological deficits
III	GCS 10 or less, with or without focal neurological deficits

GCS: Glasgow coma scale; TBME: tuberculous meningoencephalitis

Statistical analysis

Categorical variables are presented in frequency and percentage, numeric variables are presented in mean and standard deviation (normally distributed data) or median and interquartile range (IQR) (in non-normally distributed data). Patients are dichotomized into the good prognosis (GOS 4-5) and poor prognosis (GOS 1-3) groups. To determine significance, an independent t-test was conducted for normally distributed continuous variables, and Mann–Whitney U for ordinal or continuous variables with non-normal distribution. The Kolmogorov–Smirnov test for normality was done beforehand to determine normality. The Pearson chi-square test was conducted for categorical or nominal variables. Binomial logistic regression was conducted for all variables with $p<0.20$ on univariate analysis. The final model fit was assessed with the omnibus tests of model coefficients and Hosmer and Lemeshow test of good fit. All data were analyzed using IBM SPSS 26.0 for macOS.

RESULT

Demographic characteristics

64 patients with TBME were included, most were female (51.6%) with a mean age of 32 years (±18.00). 46.9% had good prognosis, 23.4% are known to have co-infection with HIV, and 65.6% had extra-CNS TB

manifestations. 15.6% of patients were on routine ATD regimens at the time of TBME diagnosis. Information regarding GCS scores, clinical features, findings on neuroimaging, treatment, MRC and GOS scores, as well as its distribution towards prognosis is listed in table 2.

Results of univariate analysis

On univariate analysis comparing variables between good and poor prognosis, significant differences were found between GCS scores (p=0.012), clinical features of meningeal irritation (p=0.004), altered consciousness (p=0.013), findings of hydrocephalus (p=0.023) and vasculitis/infarction (p=0.020) on imaging, antibiotic use (p=0.013), and MRC grading (p=0.008) Furthermore, headache (p=0.163) and glucocorticoid use (p=0.153) had p<0.2.

Results of the logistic regression analysis

Binomial logistic regression analysis was done to determine the impact of the clinical features of meningeal irritation, altered consciousness and headache, findings of hydrocephalus and vasculitis/infarction on imaging, treatment with antibiotic and glucocorticoids, and MRC grading towards the probability of good prognosis (GOS 4-5). GCS and GOS scores are excluded from analyses to avoid bias (high collinearity). Of 10 predictor variables, 4 are found to be significant: headache (OR 5.398 95% CI 1.165-25.008, p=0.031), meningeal irritation (OR 0.146 95% CI 0.026-0.813, p=0.028), hydrocephalus (OR 0.167 95% CI 0.032-0.881, p=0.035), and antibiotic usage (OR 0.155 95% CI 0.034-0.717, p=0.017). The results can be found in table

Table 2. Basic characteristics in the sample population. Patients are dichotomized into the good prognosis (GOS 4-5) and poor prognosis (GOS 1-3) groups. P-value cut-off <0.05.

Variable	All patients	Good prognosis	Poor prognosis	p (univariate)
Patients, n (%)	64 (100)	30 (46.9)	34 (53.1)	
Age, mean, (standard deviation)	32.3 (±18.00)	33.1 (±17.33)	31.62 (±18.80)	0.745
Sex				
Male, n (%)	31 (48.4)	16 (53.3)	15 (44.1)	0.462
Female, n (%)	33 (51.6)	14 (46.7)	19 (55.9)	

Glasgow coma scale at presentation				**0.012***
Compos mentis (15)	33 (51.6)	22 (73.3)	11 (32.4)	
Somnolent (13-14)	4 (6.3)	1 (3.3)	3 (8.8)	
Stupor (9-12)	21 (32.8)	6 (20.0)	15 (44.1)	
Coma (3-8)	6 (9.4)	1 (3.3)	5 (14.7)	
Clinical features, n (%)				
Fever	34 (53.1)	16 (53.3)	18 (52.9)	0.975
Headache	39 (60.9)	21 (70.0)	18 (52.9)	0.163
Nausea/vomiting	15 (23.4)	9 (30.0)	6 (17.6)	0.244
Meningeal irritation	27 (42.2)	7 (23.3)	20 (58.8)	**0.004***
Altered consciousness	34 (53.1)	11 (36.7)	23 (67.6)	**0.013***
Seizure	10 (15.6)	3 (10.0)	7 (20.6)	0.244
Focal neurological deficits	31 (48.4)	13 (43.3)	18 (52.9)	0.443
Risk factors, n (%)				
HIV/AIDS	15 (23.4)	6 (20.0)	9 (26.5)	0.542
Extra-CNS tuberculosis	42 (65.6)	21 (70.0)	21 (61.8)	0.489
Neuroimaging results, n (%)				
Tuberculoma, n (%)	11 (17.2)	6 (20.0)	5 (14.7)	0.575
Hydrocephalus, n (%)	22 (34.4)	6 (20.0)	16 (47.1)	**0.023***
Vasculitis/infarct, n (%)	9 (14.1)	1 (3.3)	8 (23.5)	**0.020***
Previous ATD treatment, n (%)	10 (15.6)	5 (16.7)	5 (14.7)	0.829
Treatment, n (%)				
Glucocorticoids	46 (71.9)	19 (63.3)	27 (79.4)	0.153
Antibiotics	42 (65.6)	15 (50.0)	27 (79.4)	**0.013***
Antiepileptics	15 (23.4)	6 (20.0)	9 (26.5)	0.542
Antipyretics	23 (35.9)	12 (40.0)	11 (32.4)	0.525
Medical Research Council grading				**0.008***
Median, IQR	2 (1.00-3.00)	1 (1.00-2.00)	2 (2.00-3.00)	
MRC 1	22 (34.4)	16 (53.3)	6 (17.6)	
MRC 2	20 (31.3)	8 (26.7)	12 (35.3)	
MRC 3	22 (34.4)	6 (20.0)	16 (47.1)	
Glasgow outcome scale				**<0.001***
Median, IQR	3 (3.00-5.00)	5 (4.00-5.00)	3 (1.00-3.00)	
GOS 1, n (%)	9 (14.1)	0 (0.0)	9 (26.5)	
GOS 2, n (%)	4 (6.3)	0 (0.0)	4 (11.8)	
GOS 3, n (%)	21 (32.8)	0 (0.0)	21 (61.8)	
GOS 4, n (%)	8 (12.5)	8 (26.7)	0 (0.0)	
GOS 5, n (%)	22 (34.4)	22 (73.3)	0 (0.0)	

AIDS: acquired immunodeficiency syndrome; ATD: anti-tuberculous drugs; CNS: central nervous system; GOS: Glasgow outcome scale; HIV: human immunodeficiency virus; IQR: interquartile range; MRC: medical research council

Table 3. Results of the binomial logistic regression model demonstrating factors associated with good prognosis (GOS4-5).

Variable	OR	95% CI	p
Clinical features			
Headache	5.300	1.157-24.282	**0.032***
Meningeal irritation	0.139	0.025-0.778	**0.025***
Altered consciousness	1.685	0.311-9.119	0.545
Neuroimaging results			
Hydrocephalus	0.192	0.038-0.972	**0.046***
Vasculitis/infarct	0.118	0.010-1.442	0.094
Treatment			
Glucocorticoids	1.586	0.334-7.534	0.562
Antibiotics	0.167	0.038-0.728	**0.017***
MRC grading (benchmark MRC 1)			0.197
MRC 2	0.373	0.050-2.796	0.337
MRC 3	1.812	0.255-12.796	0.552

MRC: medical research council

DISCUSSION

Of 64 patients, 46.9% are discharged with a good prognosis (GOS 4-5), with the capacity to conduct daily activities independently. The rate of mortality in our study is 14.1%. 23.4% of patients were co-infected with HIV, and 65,5% had coexistent extra-CNS manifestations of TB. 15.6% were routinely consuming ATDs at the time of TBME diagnosis, but this fact had no significant effects on prognosis. On logistic regression, clinical features of meningeal irritation and altered consciousness, hydrocephalus, as well as antibiotic use was significantly associated with poor prognosis, whereas presence of headaches were associated with better prognosis. On univariate analysis, evidence of vasculitis/infarction on neuroimaging and greater MRC severity also demonstrated significance. These findings are consistent with results from previous studies stating that altered consciousness, greater MRC severity, and hydrocephalus was associated with poor prognosis.[10–12] Advanced age and co-presence of extra-CNS TB was also associated with poor prognosis in some studies,[10,12] although we did not find this association in our results, nor in similar studies.[11]

Presence of signs of meningeal irritation, as characterized by nuchal rigidity and the Kernig and

Brudzinski signs, as well as altered consciousness, is significantly associated with poor prognosis in TBME patients. The pathomechanism underlying meningeal irritation has not yet been fully understood. It is thought that passive neck flexion causes movement of the spinal cord and stretching of the meninges, inducing pain in patients with meningitis, wherein nuchal rigidity and hip and knee flexion serves as compensatory mechanisms to alleviate pain and meningeal irritation.[13] A systematic review by Akaishi et al. found that signs of meningeal irritation is negative in approximately half of all meningitis patients, with the sensitivity of nuchal rigidity at 40-60%, and that of the Kernig and Brudzinski signs lower at 20-30%. However, the Kerning and Brudzinski signs demonstrate greater specificity (85-95%) compared to the former two (65-75%).[14] Therefore, it is thought that presence of meningeal irritation increases with disease severity and may indicate the presence of a more generalized or intense inflammatory process associated with poor prognosis.

As with meningeal irritation, findings of vasculitis, infarction, and hydrocephalus demonstrates presence of further complications and a more severe/generalized infection with increasing severity and is linked with poor prognosis. A pathological hallmark of TBME is the formation of thick exudates in the basal cisterns, coating and irritating the optic chiasm and nerve, blood vessels, and other passing cranial nerves, and may obstruct the flow of cerebrospinal fluid (CSF), causing hydrocephalus.[6,15,16] Hydrocephalus is commonly associated with increased intracranial pressure (ICP) and a number of other complications. If left alone, elevated ICP can result in loss of consciousness, compression of blood supply, and cause infarction.[16] The optic nerve can be compressed as a result of third ventricle enlargement and may eventually lead to optic nerve atrophy.[17] As hydrocephalus is associated with poor prognosis, its management constitute an important issue. However, indications regarding ventriculoperitoneal shunt placement or CSF drainage remains controversial with unclear benefits

and risks of complication.[18–21] Vasculitis is a severe complication often seen in TBME, and its presence indicates severe disease. Vasculitis can lead to infarction and permanent ischemic sequelae. Infarctions in the context of TBME is caused by arteritis and large vessel compression by tuberculous exudates leading to arterial vasospasm or thrombosis. However, strategies for the prevention and treatment of meningitis-associated infarction remains unclear.[22,23] Interestingly, while the proportion of seizures observed in our study is much higher in the poor prognosis group (20%) compared to the good prognosis group (10%), we did not find a significant relationship on analysis, possibly due to our relatively small volume of sample.

We observe that headache is associated with better prognosis, in concert with findings by Lu et al.[11] Presence of headaches may prompt the patient to present earlier to the hospital. It is also likely that patients complaining of headache remains alert and conscious, while patients without these complaints have already experienced altered consciousness and is unable to convey their complaints and seek medical assistance.

Administration of additional antibiotics (non-tuberculous antibiotics) are significantly associated with worse outcome. A confounding factor may be present in this regard, as patients with a worse clinical outlook may prompt the clinician to prescribe additional antibiotics due to suspicion of a secondary infection. However, this demonstrates that the addition of prophylactic antibiotics for secondary infection is non-beneficial and does not contribute to improving prognosis in cases of TBME. Several previous studies found that glucocorticoid treatment was associated with better prognosis. Glucocorticoids are beneficial in ameliorating cerebral edema and inflammatory exudates.[10,11,24] While we did not see such benefit in our study, this may be due to routine administration of steroids in both prognosis groups, and our study design did not account for the specific agent, duration, and dose of steroid administration. Therefore, we cannot adequately evaluate the effects of steroid administration.

Limitations in our study includes its relatively modest sample size. Furthermore, data collection was retrospective, and our analysis is limited to the information recorded in the medical record. The authors recommend further studies be conducted to evaluate prognostic factors in TBME, particularly with additional analyses involving CSF findings (including bacilli isolation/results of nucleic acid amplification test), duration between onset of symptoms and treatment, and steroid therapy.

CONCLUSION

In conclusion, clinical features of meningeal irritation and altered consciousness, imaging findings of hydrocephalus and vasculitis/infarction, and antibiotic usage is associated with poor prognosis, while presence of headache is associated with a better prognosis.

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