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FACTORS AFFECTING PROGNOSIS OF TUBERCULOUS MENINGITIS

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ABSTRACT

Background: The mortality rate of tuberculous meningitis (TBM) is approximately 20-41%. The prognosis is influenced by clinical and radiological features, laboratory findings, and therapy.
Objective: To report factors affecting the prognosis of TBM patients in Dr. Saiful Anwar Hospital.
Methods: The study design was a retrospective cohort with consecutive sampling. Data were collected from medical records of 47 patients from 2016-2017. Researchers used modified Rankin Scale (mRS) as prognostic value (good prognosis (mRS 0-2) and poor prognosis (mRs 3-6). The impact of clinical, radiological, and laboratory factors were analyzed by univariate analysis and multiple logistic regression.
Results: In this study, good (n=21) and poor (n=26) prognosis were compared. Patients with good prognosis experienced more episodes of seizure than poor prognosis (17% vs 4%; p = 0.011). Focal neurologic deficits were more frequent in poor prognosis (4% vs. 23%, p = 0.012). Meningeal enhancement was more common in poor prognosis (21% vs 42%; p= 0.038). From multivariate analysis, researchers found that seizure and focal neurological deficit are independent prognostic factors (p=0.023 and p 0.033).
Conclusion: Clinical factors influencing prognosis of TBM in Dr. Saiful Anwar Hospital are seizure and focal neurological deficit. Focal neurological deficit is a poor prognostic factor.

Keywords: Prognostic factors, tuberculous meningitis

Introduction

Mycobacterium tuberculosis infection is still being global epidemic especially in Asia. In 2006, 9.2 billion new incidences have been found and the death is about 1.7 billion due to tuberculosis. In 2009 TB case increase to become 9.4 billion cases which is equivalent to 137 per 100.000 population.[1]

Tuberculous meningitis (TBM) is a fatal complication of tuberculosis infection which frequently causing permanent disabilities for patient. This disease is the fifth most frequent extra pulmonary TB form and is about 5.2 % of the total case of extra pulmonary TB. In USA, TBM is approximately 3% while in Philippines is about 28.9%.[2,3] Mortality rate is about 20-41 %.[4] High mortality and morbidity rate is usually caused by the delay of diagnosis as researchers know that the clinical and radiological manifestation varies among the patients.[1,5,6]

Prognosis of TBM has been influenced by several factors. Clinical stadium and 'time to give the treatment' have been found to be the factors. Onset of age, severity, Glasgow coma scale (GCS), TB outside CNS, and finding of *M. tuberculosis* in CSF (*cerebro spinal fluid*), biochemical analysis, hidrosefalus and infarction were some of the factors studied.[7,8]

TBM infection has unknown onset when affect someone and the manifestation is not typical and varies. That is one of the reason why researchers find the case with the late and severe stage of the disease, thus the effective treatment cannot be achieved resulting high mortality rate. Moreover, the bacteria develop resistance to antibiotics and the concomitant infections of HIV-TB make the mortality increase.[8,9] To know what factors affecting prognosis of TBM, researchers conduct this research retrospectively in Dr. Saiful Anwar General Hospital Malang.

Methods

The design of this research was cohort retrospective. Data were collected from 47 medical record of patient since 2016 until 2017. Samples were collected by consecutive sampling method. Population includes all patients TBM in Dr. Saiful Anwar Hospital. The patients who meet inclusion criteria were included in the research. Inclusion criteria: age more than 18, diagnosis TBM at discharge, diagnosis made by the Lancet criteria. Exclusion criteria: patient with inflammation due to autoimmune disease, malignancy, recurrent TBM after discharge. Initial data of clinical, radiological and laboratory data were collected. Prognosis was evaluated by modified Rankin Scale (mRS) at discharge. Score MRS 0-2 was categorized as good prognosis meanwhile 3-6 categorized as poor prognosis. These factors affecting prognosis then were analyzed using univariate analysis. Significant factors then were analyzed by multiple logistic regressions. Data analysis used SPSS 19.0.

Results

Clinical profiles of patients were age, gender, fever, neck stiffness, seizure and focal deficits. Researchers summarized the clinical profile in the table 1.

Table 1. Clinical characteristic of Meningitis Tuberculosis.

Variables	Total patients (n= 47)
Age < 60 y.o	45 (96%)
Male gender	31 (66%)
Febrile >37.5°C	28 (60%)
Headache	36 (76.6%)
Neck Stiffness	46 (98%)
Seizure	10 (21%)
Focal deficits	13 (27%)
HIV positive	5 (10%)
Definite Meningitis TB	1 (2%)
Probable Meningitis TB	23 (49%)
Possible Meningitis TB	23 (49%)
Mild Stage	5 (10%)
Moderate Stage	23 (49%)
Sever Stage	19 (41%)

Radiological imaging was performed using CT scan or MRI with contrast. The results of radiology finding of meningitis tuberculosis were given in the Table 2.

Table 2. Radiological finding of Tuberculous Meningitis.

Variables	Total patient (n= 47)
Meningeal enhancement	30 (64%)
Hydrocephalus	22 (47%)
Tuberculoma	8 (17%)
Infarct	9 (19%)

Researchers devided prognosis as good and poor prognosis based on Modified rankin scale (mRS) score. Clinical, radiological, and laboratory data were compared between good prognosis and poor prognosis. Prognostic factor was shown in Table 3 and 4. Researchers found that there were no significant laboratory factors between good and poor prognosis.

Factors with p value <0.05 (seizure, focal deficits and meningeal enhancement) from univariate analysis result were analyzed with logistic regression model. Focal deficits and seizures were independent risk factors for prognosis of tuberculous meningitis. Multivariate logistic regression analysis was shown in Table 5.

Table 3. Laboratory result of Tuberculous Meningitis.

Factors	Prognosis		P value
	Good	Poor	
Estimated sedimentation rate (mm/jam)	43.524 ± 25.541	42.731 ± 17.049	0.899
Serum Sodium level (mmol/L)	129.190 ± 7.215	128.308 ± 10.380	0.743
Leucocyte in CSF (sel/µL)	61.667 ± 99.239	122.308 ± 165.971	0.148
Lymphocyte in CSF (sel/µL)	57.524 ± 87.145	87.385 ± 116.193	0.334
Protein in CSF (mg/dL)	144.286 ± 79.077	159.900 ± 107.722	0.582
Glucose ratio CSF : serum	0.346 ± 0.189	0.294 ± 0.241	0.424
Lactate dehydrogenase CSF (IU/L)	171.333 ± 122.819	285.000 ± 266.959	0.078

Table 4. Clinical and radiological factors for prognosis of TBM.

Factors	Prognosis		Total n = 47	P value
	Good	Poor		
Age < 60 y.o	21 (44%)	24 (51%)	45 (95%)	0.194
Male	13 (27%)	18 (38%)	31 (65%)	0.598
Febrile > 37.5°C	11 (23%)	17 (36%)	28 (59%	0.366
Neck stiffness	20 (42%)	26 (55%)	46 (97%)	0.261
Seizure	8 (17%)	2 (4%)	10 (21%)	0.011
Focal deficits	2 (4%)	11 (23%)	13 (27%)	0.012
Meningeal enhancement	10 (21%)	20 (42%)	30 (63%)	0.038
Hydrocephalus	8 (17%)	14 (29%)	22 (46%)	0.282
Tuberculoma	3 (6%)	5 (10%)	8 (16%)	0.654
Infarct	3 (6%)	6 (12%)	9 (18%)	0.446
HIV positive	1 (2%)	4 (8%)	5 (10%)	0.24
Definite TBM	0 (0%)	1 (2%)	1 (2%)	
Possible TBM	10 (21%)	13 (27%)	23 (48%)	0.633
Probable TBM	11 (23%)	12 (25%)	23 (48%)	
Mild Stage	3 (6%)	2 (4%)	5 (11%)	
Moderate stage	12 (25%)	11 (23%)	23 (48%)	0.314
Severe stage	6 (12%)	13 (27%)	19 (39%)	

Table 5. Multivariate Logistic Regression Analysis of prognostic factors in TBM.

Risk factors	Odds ratio (95%CI)	P value
Seizure	16.427	0.023
Focal Deficits	0.086	0.033
Meningeal enhancement	0.408	0.234

Discussion

From this study researchers found 21 patients (45%) with good prognosis and 26 patients with poor prognosis. Based on clinical profiles, the mean of onset age was 34 years old. Patients more than 60 years old were only two patients. This finding was similar with study by Gu et al., 2015 which revealed that the mean onset of age was 33 years old.[8] Gu et al., also stated that patient more than 60 years old (38 patients (63%)) was significant prognosis factor. [8] Other study stated that age more than 40 years old was poor prognosis for patients.[9] Meanwhile age was not significant prognostic factor to tuberculous meningitis in our study (p=0.194). the difference of result was due fto only 2 patients (4%) found more than 60 years old in our hospital. Genetic factor such as TLR gen and LTA4H gen has been found to make the young adult more susceptible to TBM and also malnutrition, higienity might be contributing factor.[10]

Male gender was found to have TBM more frequent than female (31 patients /66%). This was similar with study to said that affected male were 98 patients (65%). Other study stated male with TBM were 71 orang (62%).[4,8] There was no

significant differences between male and female in affecting prognosis of tuberculous meningitis.

In this study focal deficits gave significant differences in affecting prognosis of tuberculous meningitis. Patient with focal deficits who had poor prognosis were 13 (55%) with p value = 0.012. Multivariate analysis showed that focal deficits were factors affecting poor prognosis of TBM with p value = 0.033. Focal deficits involved cranial nerve palsy and hemiparesis. The most common cranial nerve palsy in patient with TBM were III, VI and VII cranial nerve palsy.[3] in this Study, researchers found that VI nerve palsy was the most frequent. Cranial nerve palsy in TBM is usually caused by tubercle in ganglia basal area which leads to inflame the nerve. This inflammation process produce proinflammatory cytokine such as TNF-α, interleukin 1β which trigger apoptotic process in brain cells.[11] Focal deficits can also be caused by intracranial vasculitis. Vasculitis is severe abnormality in TBM which can involve small vessel, medium as well as large vessel. Vasculitis can occlude the blood vessel partially or totally. Vasculitis often occurs in area of Circle of Willis. Middle or anterior artery is mostly affected areas which show inflammatory, proliferative and degenerative changes. The involvement of adventitia such as cellular infiltration with or without tubercle and necrosis formation explains expansion of tuberculosis infection from subarachnoid space.[3,5] This study showed that focal deficits were poor prognostic factor to TBM patient. It might be caused by severe vasculitis or inflammation that spread to brainstem area where nerve's roots exit.[4,9]

Imaging results such as meningeal enhancement, infarction, hydrocephalus and tuberculoma were analysed too. Radiographic finding of TBM are varies and not specific. In the initial phase of TBM, it shows exudative lesion and meningeal enhancement whereas in late phase, hydrocephalus can be found. MRI is more sensitive to show the lesion than CT especially for brainstem and meningeal lesion. Santy et al, 2011 stated that TBM MRI lesion will increase lipid peak so it can differentiate whether it is tuberculous or nontuberculous infection.[12] Our study showed that meningeal enhancement gave significant differences in TBM prognosis by univariate analysis (p=0.038). From logistic regression analysis, this variable is not prognostic factor for TBM. Hsu et al, stated that hydrocephalus was found in 44 patients (75.9%). It was poor prognosis factor in TBM (p=0.000). Gu et al., stated that hydrocephalus was poor prognostic factor for TBM (p=0.016).[8] Those studies did not include meningeal enhancement as factor to be analysed. In our study showed that hydrocephalus occurred in 14 patients (63%) with poor prognosis. This factor was not significantly associated with poor prognosis of TBM (p=0.282). The different result might be caused by the different quantity of samples. In addition to that, different time (initial or late phase) in taking the MR or CT image might give different result.

Our study showed that stage of TBM was not significantly associated with prognosis (p= 0.314). Gu et al., 2015 revealed that stage of TBM was significantly associated with prognosis. Stage TBM was poor prognostic factor (p=0.038). Initial Glasgow Coma Scale (GCS) was also poor prognostic factor.[8] Other study revealed that there was significant association between stage of TBM and poor prognosis (p=0.006), which stage III (severe) had higher chance of mortality than in stage I, however no significant differences between stage I and stage II. Other study which involved 160 patients, showed that stage III patient (69%) were dead. Late stage had significant association with mortality in univariate analysis (p=0.001).[9] The difference result might be caused by different samples number. Those two studies used mortality as prognosis to be evaluated, whereas our study used modified Rankin Scale as prognosis of TBM. mRS score 3 – 6 were counted as poor prognosis so that deceased patients were included in this category. This was also associated with classification of TBM which those studies had definitive TBM patients more frequent than in our study. Mortality in those studies evaluated 12 months later while our study only evaluated prognosis at discharge which was only 1 month. This might cause insignificant result of TBM stage to prognosis which outcome after one month was not evaluated where complication could be still happened to patients.

The interesting result of this study came from seizure factor. researchers found 10 patients with seizure. 8 patients showed good prognosis meanwhile 2 patients had poor prognosis. Our study revealed that seizure has been reported to be good predictor for TBM by logistic regression analysis (p= 0.023). This result was different with previous study by Misra et al. who stated that seizures occurred in 34% patients with TBM and were associated with poor outcome at six months. Seizures occurred in 27 (34.2%): early onset in 8 (29.6%) and late in 19 (70.4%) patients. The seizures were focal in 11(13.9%), focal to bilateral in 9 (11.4%), generalised tonic clonic in 7 (8.9%) and status epilepticus in 6 (7.6%) patients. Early seizures were associated with meningeal irritation and late seizures with tuberculoma, infarction and hyponatremia (P = 0.01). Seizure did not affect the mortality but were associated with worse six months' outcome (P = 0.03).[13]

Seizure can be occurred in patient with TBM. The incidence is 17-93%. The underlying cause is multifactorial. The increase of intracranial pressure, cerebral edema, meningeal irritation, tuberculoma and ischemic lesion have been found to be the causes. Seizure type is also varying. It can be focal motor seizure or general tonic clonic seizure. Nonconvulsive status epilepticus also can be found.[14,15] This study found that all patients with seizure (10 patients) had general tonic clonic seizure. While other study stated that there 19 patients had seizure in TBM with hyponatremia.[16] Brigo et al., 2012 revealed that there were 101 out of 136 patients TBM who had seizure. The most frequent seizure was general tonic clonic (58%), focal seizure (38%) and tonic seizure (4%). The underlying cause of this seizure were cerebral edema 58 patient (57%), Hyponatremia 48 patients (47.5%), SIADH 35 patients (35%), hydrocephalus 32 patients (32%), tuberculoma 27 patients (27%), abnormal focal discharge (25%), and cerebral infarct (13%).[15]

The causes of seizure in this study could be from increase of intracranial pressure or extracranial problem such as hyponatremia. From 8 patients with good prognosis who had cerebral edema, 6 of them also had moderate to severe hyponatremia. Good prognosis at discharge might be supported by good and adequate treatment of cerebral edema and hyponatremia. Cerebral edema, hyponatremia and SIADH are transitory in nature which responsive to treatment.[15,16] 5 out of 8 patients had hydrocephalus moderate to severe. 4 patients had been done external ventricular drainage. Gu et al., 2015, stated that EVD gave no significant association with outcome of patients TBM (p=0.280). But the

steroid did ($p<0.001$).[8] Almost of the patients got steroid treatment based on stage of BMRC. Seizure in TBM must also be evaluated in EEG to help the diagnosis.

Conclusion

Clinical factors which affected to prognosis were seizure and focal deficits. Focal deficits were poor prognostic factor meanwhile seizure was good prognostic factor. Laboratory and radiographic result were not prognostic factor for TBM in Dr. Saiful Anwar General Hospital Malang.

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