The Mortality of Tuberculous Meningitis in Maharat Nakhon Ratchasima Hospital

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Abstract

Objective: Tuberculous meningitis (TBM) is one of the most severe manifestations of extrapulmonary tuberculosis and is associated with severe morbidity and high mortality. To evaluate mortality rate and mortality-related factors of TBM in Maharat Nakorn Ratchasima hospital.

Method: This retrospective study was conducted in a large tertiary-care hospital including 191 patients with TBM. Mortality was defined as death during hospital admission.

Result: There were 191 cases in this study and 136 patients (71.2%) were male. The mean age was 41.8 years old (SD ±15.53). HIV Infected patient is 56 (29.3%). In-hospital mortality rate of TBM was 13.1% (25 patients). The mortality-related factors were as follows: age >40 ($p<0.01$, HR 3.91, 95%CI: [1.4-10.9]), onset <7 days ($p=0.02$, HR 2.64, 95%CI: [1.12-6.2]), fever ($p<0.01$, HR 2.52, 95%CI: [1.07-5.94]), neck stiffness ($p=0.01$, HR 3.3, 95%CI: [1.2-9.2]), altered consciousness (GCS≤14) ($p<0.01$, HR 2.04, 95%CI: [1.53-2.72]) and BMRC severity grade II and grade III ($p<0.01$). The radiological abnormalities that associated with poor outcome were hydrocephalus ($p<0.01$, HR 3.69, 95%CI: [1.55-8.78]) and cerebral infarction ($p=0.08$, HR 2.71, 95%CI: [0.88-8.34]).

Conclusion: The mortality rate of TBM in Maharat Nakhon Ratchasima hospital was 13.1%. The mortality-related factors were elderly, rapid onset, fever, neck stiffness, altered consciousness and BMRC severity grade II and III, low serum sodium, low CSF total WBC count, low CSF glucose-serum ratio, hydrocephalus and cerebral infarction. When clinical is suspected of TBM, the prompt diagnosis and empirically treatment can reduce morbidity and mortality of TBM.

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Introduction

Tuberculosis is the leading infectious cause of death worldwide.[1] Tuberculous meningitis (TBM) is the major cause of death and is one of the most severe manifestations of extrapulmonary tuberculosis. TBM is associated with severe morbidity and high mortality of extrapulmonary tuberculosis.

TBM is occurred by a slowly progressive granulomatous inflammation of the basal meninges. The inflammation can lead to many complications, such as hydrocephalus, cerebral infarction, cranial nerve palsy and death. Rapid diagnosis and initiation of treatment is therefore necessary to reduce the mortality and sequelae associated with TBM. Diagnosing TBM can be difficult because the symptoms are unspecific and mimic other meningitis or other cerebrovascular events.[2] High mortality and morbidity are related to delay diagnosis and treatment due to non-specific manifestation and lack of concern.[3-5] Late sequalae of TBM include cranial nerve palsies, gait disturbance, hemiplegia, blindness, deafness, learning disabilities, dementia, and syndromes of hypothalamic and pituitary dysfunction.[6]

World Health Organization (WHO) classified Thailand as one of the 30 countries with the highest TB burden, Thailand had estimated TB incidence of 153 per 100,000 population.[1] There are limited number of previously published clinical studies on baseline characteristic, clinical manifestation, imaging, CSF analysis of TBM.[7-9]

Maharat Nakhon Ratchasima hospital is the largest regional tertiary-care center in Thailand. Many difficult and complicated cases are referred for specialized care. The aim of this study was to describe in-hospital mortality rate and mortality-related factors of TBM in Maharat Nakhon Ratchasima hospital. In addition, the authors describe the clinical profile, laboratory finding, imaging abnormalities and clinical outcome. Only limited number of studies were carried out in Asian population and developing countries. Thus, the authors expected that the result of this study can lead to increase diagnosis awareness of TBM and prescribe urgent treatment for improving the outcome of TBM patients in Maharat Nakhon Ratchasima hospital.

Material and Methods

Study populations

A retrospective study was conducted from January 1st, 2014 to December, 31th 2019 at Maharat Nakhon Ratchasima hospital, Nakhon Ratchasima, Thailand. The medical records of adult patients, aged more than 18 years with provisional diagnosis of TBM upon admission to the hospital, were reviewed.

Methods

Inclusion criteria were: (1) age ≥ 18 years (at the time of admission) both male and females, (2) diagnosed as TBM using clinical data (definite, probable, and possible TBM were included), and (3) admitted to Maharat Nakhon Ratchasima hospital within the period of study. Exclusion criteria were: (1) meningitis caused by viruses, protozoa, fungi or bacteria other than *Mycobacterium tuberculosis*, (2) medical records are not available or incomplete data, and (3) the patient who was given alternative diagnosis.

In this study, the clinical diagnosis of TBM was made by symptoms (fever, headache, nausea and

vomiting, focal neurological deficit), clinical signs (stiffness of neck, cranial nerve palsy, focal neurological deficits, and altered mental status), radiological study consistent with TBM (leptomeningeal enhancement, hydrocephalous, abscess or tuberculoma), and/or positive microbiological or molecular evidence of mycobacterium in CSF. Definite TBM was defined by: (1) positive microbiological or molecular evidence of MTB from CSF or consistent histopathological reports of brain tissue; or (2) positive microbiological or molecular evidence of MTB from any organs, or chest radiography compatible with active pulmonary TB together with clinical suspicion of TBM. Possible TBM was defined as patients with a provisional diagnosis of TBM in the absence of criteria for definite TBM, and no identified alternative causes.[10,11] All study population received at least 9 months of anti-TB drugs and standard regimen of systemic steroid.[2]

Clinical evaluation of the stage of TBM is mostly according to the criteria of the Medical Research Council (BMRC criteria): BMRC stage I (non-specific symptoms, with little or no clinical signs of meningitis, with no paresis, in good general condition, and fully conscious), BMRC stage II (condition between those of stage I and III), and BMRC stage III (advanced stage, extremely ill, deeply stuporous or comatose, or with gross paresis).[12]

Data collections

The collected data included demographics, sex, age, HIV status, symptom duration, clinical signs, symptoms, BMRC severity grading, extra-cerebral TB manifestation, serum sodium, serum albumin, CSF profiles, radiological abnormalities including complications. The outcome was divided into death and survive. The association between the outcomes and related factors were analyzed.

Statistical analysis

The descriptive data were presented as frequency, percent, mean ± standard deviation (SD) and median with interquartile range (IQR). The association between outcomes and related factors were analyzed by using Chi-square or Fisher's exact test in non-continuous data and student's t-test or Mann-Whitney U test for continuous data. Odd ratio (OR) or hazard ratio (HR) and 95% confidence intervals (95% CIs) were used to demonstrate the association between related factor and outcomes. A p-value of <0.05 was considered statistical significance.

Results

This study included 191 patients with a diagnosis of TBM. Demographic and clinical data are shown in Table 1. There were 191 patients in this study and 136 patients were male (71.2%). The mean age was 41.8 years old (SD ±15.53). HIV Infected were found in 56 patients (29.3%). General and neurological symptoms were: fever (77 patients, 40.3%), headache (144 patients, 75.4%), nausea/vomiting (37 patients, 19.4%), neck stiffness (111 patients, 58.1%), focal neurological deficit or limb weakness (19 patients, 9.9%) and cranial neuropathy (4 patients, 2.1%). Laboratory and radiological investigation are shown in Table 2. Evidence of MTB genetic material in CSF was positive only 40 cases of 191 patients (20.9%). Chest radiography, chest CT, and/or sputum examinations were consistent with active pulmonary TB in 48 patients (25.1%). There was evidences of TB pleuritis in 14 patients

(7.3%) and evidence of TB lymphadenitis was founded in 9 patients (4.7%). There was no evidences of TB pericardium and TB peritonitis in this study.

The In-hospital clinical outcomes were shown in Table 3. In-hospital mortality rate was 13.1% (25 patients). The most common causes of death are hospital acquired pneumonia (not shown on the table). The other complications were; hydrocephalous (63 patients, 33%), cerebral infarct (19 patients, 9.9%), cranial neuropathy (4 patients, 2.1%) and hyponatremia (118 patients, 61.8%).

The factors that associated with mortality were shown in Table 4. The statistical significance related clinical factors were: age ≥40 (p<0.01, HR 3.91, 95%CI: [1.4-10.9]), onset < 7days (p=0.02, HR 2.64, 95%CI: [1.12-6.2]), fever (p<0.01, HR 2.52, 95%CI: [1.07-5.94]), neck stiffness (p=0.01, HR 3.3, 95%CI: [1.2-9.2]), altered consciousness (GCS≤14) (p<0.01, HR 2.04, 95%CI: [1.53-2.72]) and BMRC severity grade II and grade III (p<0.01). The radiological abnormalities that associated with poor outcome were hydrocephalus (p<0.01, HR 3.69, 95%CI: [1.55-8.78]) and cerebral infarction (p=0.08, HR 2.71, 95%CI: [0.88-8.34]).

The laboratory investigations that associated with mortality were: hyponatremia, CSF glucose/serum glucose ratio and CSF WBC count. The mean of serum sodium in death cases, 123.8 meq/L was lower than in survived cases, 128.5 meq/L (p<0.01). The mean CSF WBC count in survived cases was 141.41 cells x 10^9 /L and 97 cells x 10^9 /L in death cases (p=0.03). The mean CSF glucose/serum glucose ratio was 0.28 in survived cases and 0.19 in death case (p<0.01).

Table 1 Baseline characteristic (191 patients)

Clinical profile	Number (%+)
Sex	
- Male	136 (71.2%)
Age, Mean ± SD (years)	41.58 ± 15.53
- ≥ 40 years	104 (54.5%)
HIV infected	56 (29.3%)
Onset of symptoms, mean ± SD (days)	10.89 ± 11.58
General and neurological Symptoms	
- Fever	77 (40.3%)
- Headache	144 (75.4%)
- Nausea/vomiting	37 (19.4%)
- Seizure	18 (9.4%)
- Neck stiffness	111 (58.1%)
- Altered consciousness or GCS≤14	49 (25.6%)
- Focal neurological deficit	19 (9.9%)
- Cranial neuropathy	4 (2.1%)
BMRC severity grade	
- Grade I	142 (74.3%)
- Grade II	44 (23%)
- Grade III	5 (2.6%)

Table 1 Baseline characteristic (191 patients) (cont.)

Clinical profile	Number (%+)
Extra-cerebral TB manifestations	
- Pulmonary	48 (25.1%)
- Pleura	14 (7.3%)
- Lymph node	9 (4.7%)

Abbreviations: GCS, Glasgow Coma Scale, SD, standard deviation, BMRC, British Medical Research Council. + Percent from all of 191 patients.

Table 2 Laboratory and radiological investigation findings

Blood result, Mean (±SD)	
- Serum sodium	127.93 (±7.2)
- Serum albumin	3.43 (±0.52)
Cerebrospinal fluid, median (IQR)	
- Opening pressure (cmH_2O)	14 (12-24)
- Total protein (g/L)	251 (149-330)
- CSF glucose/ serum glucose ratio	0.25 (0.17-0.33)
- White blood cells (cells x 10^9/L)	63 (18-149)
- Lymphocyte predominate	134 (70.2%+)
- Positive CSF PCR for TB	40 (20.9%+)
Radiological abnormalities	
- Leptomeningeal enhancement	74 (38.7%+)
- Hydrocephalus	63 (33%+)
- Tuberculoma/abscess	43 (22.5%+)
- Cerebral infarct	19 (9.9%+)

Abbreviations: SD, standard deviation, IQR, Interquartile range, Cerebrospinal fluid, PCR, Polymerase chain reaction. + Percent from all of 191 patients.

Table 3 In-hospital clinical outcome (191 patients)

Clinical outcome	Number (%+)
- Death	25 (13.1%)
- Survive	166 (86.9%)
Complications from the disease	
- Hydrocephalus	63 (33%)
- Cerebral infarct	19 (9.9%)
- Cranial neuropathy	4 (2.1%)
- Hyponatremia (≤130 meq/L)	118 (61.8%)

Abbreviations: IQR, interquartile range, meq/L, Milliequivalents per litre. + Percent from all of 191 patients.

Table 4 Factors associated with mortality in TBM

Factors	Mortality rate		p-value	HR (95% CI)
	Survive 166 (86.9%)	Death 25 (13.1%)		
Age				
- ≥40 years	84	20	<0.01	3.91 (1.40-10.90)
Sex				
- Male	121	15	0.14	0.56 (0.23-1.33)
HIV infected	56	0	<0.01	0.66 (0.59-0.74)
Symptoms duration <7 days	54	14	0.02	2.64 (1.12-6.20)
General and neurological symptoms				
- Fever	62	15	<0.01	2.52 (1.07-5.94)
- Headache	124	20	0.38	1.36 (0.48-3.84)
- Nausea/vomiting	32	5	0.56	1.05 (0.37-3.00)
- Seizure	18	0	0.07	0.89 (0.85-0.94)
- Neck stiffness	91	20	0.01	3.30 (1.20-9.20)
- Altered consciousness or GCS<14	24	25	<0.01	2.04 (1.53-2.72)
- Focal neurological deficit	14	5	0.08	2.71 (0.88-8.34)
- Cranial neuropathy	4	0	0.57	0.98 (0.95-1.00)
BMRC severity grade				
- Grade I	142	0		
- Grade II	24	20	<0.01*	
- Grade III	0	5	<0.01*	
Extra-cerebral TB manifestations				
- Pulmonary	43	5	0.36	0.72 (0.25-2.02)
- Pleuritis	14	0	0.13	0.92 (0.87-0.96)
- Lymph node	9	0	0.28	0.95 (0.91-0.98)
Serum sodium (mean, meq/L)	128.55	123.80	<0.01	
Serum albumin (mean, g/dL)	3.39	3.72	<0.01	
CSF Finding (mean)				
- Open pressure (cmH_2O)	17.59	21.00	0.11	
- Total protein (g/L)	297.75	325.20	0.55	
- CSF glucose/ serum glucose ratio	0.28	0.19	<0.01	(0.05, 0.14)
- White blood cells (cells x 10^9 /L)	141.41	97.00	0.03	(4.06, 84.76)
- Lymphocyte predominate (Number)	124	10	<0.01	4.43 (1.85-10.6)
- Positive CSF PCR for TB (Number)	30	10	0.02	3.02 (1.24-7.38)
Radiological abnormalities				
- Leptomeningeal enhancement	64	10	0.53	1.06 (0.45-2.51)
- Hydrocephalus	48	15	<0.01	3.69 (1.55-8.78)
- Tuberculoma/abscess	43	0	<0.01	0.74 (0.68-0.81)
- Cerebral infarct	14	5	0.08	2.71 (0.88-8.34)

Abbreviations: HR, hazard ratio, CI, confidence interval. *compared to BMRC grade I

Discussion

The mortality rate of TBM in Maharat Nakhon Ratchasima was 13.1% which was lower than other previous studies. The study of Pleumpanupat P, et al showed the mortality rate of TBM was 54.5% and factors related that correlated with poor outcome were BMRC severity grading, imaging abnormalities, HIV infection, serum sodium and time to ARV initiation.[7] The study of Kirdlarp S, et al showed the mortality rate was 17.7% and factors associated to mortality were older age and HIV coinfection.[4] In Denmark, the overall mortality rate of TBM was 19% and 48% of the remaining patients had neurological sequelae of varying degree.[13] The study of clinical features and outcome in 75 adult cases of TBM in Madagascar showed that the mortality rate was 28% and occurred early after admission.[14] Age more than 35 years and coma predicted inpatient mortality.[14] Most of patient in these studies presented with advanced clinical stage (BMRC grades II and III), unlike our study in which most patients come relatively early in the early stages (74% of patients, BMRC grade I). Duration of symptom prior to admission reported in previous studies was commonly longer than 1-2 weeks which was consistent with subacute meningitis.[13-16] However, duration of symptoms prior to admission in our study was substantially shorter than reported in other studies.

There were other reasons that mortality rate was low in our study. First, this study excluded the patients who had multiple CNS infection, also excluded the patients who was diagnosed with TBM from primary-care or rural hospitals. The number of HIV infected patient was excluded due to provisional diagnosis of multiple CNS infection e.g., cryptococcal meningitis, bacterial meningitis and/or cerebral toxoplasmosis in which the patients may be infected with TBM along with other co-CNS infection. Second, the major limitation of our study was lack of information on long term outcomes after discharge and the number of given telephone number in data recorded was no longer used. Third, this study included only in-hospital death. Forth, the patients who were readmitted after being diagnosed with TBM in previously visit were excluded.

From the previous literatures, the populations in each study had high variability because of differences in methodology, study design, study population, level of hospital, medication, medical facilities, follow-up period and the definition of TBM.

One of the observations in our study is that the majority of the patients were male (71.2%), which was not found in other studies without the obvious reason. The mortality related factors which same as previous study were BMRC severity and lower of serum sodium. We found that lower CSF WBC count was associated with mortality which is close to the study of Phong L, et al which found that lower CSF lymphocyte count was related to high mortality.[11] In our study, lower CSF/serum glucose ratio was related to the mortality rate, same as previous study.[17]

This study found that only 40% of patients had fever. Therefore, if the patient has suspected symptoms even without fever, the clinician should be aware of TBM.

Conclusion

The mortality rate of TBM in Maharat Nakhon Ratchasima hospital was 13.1%. The mortality-related factors were elderly, rapid onset, fever, neck stiffness, altered consciousness and BMRC severity Grade II and III, low Serum sodium, low CSF total WBC count, low CSF glucose-serum ratio, hydrocephalus and cerebral infarction. When

clinical is suspected of TBM, the prompt diagnosis and empirically treatment can reduce morbidity and mortality of TBM.

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