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Old age and hydrocephalus are associated with poor prognosis in patients with tuberculous meningitis

A retrospective study in a Chinese adult population

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Abstract

Tuberculous meningitis (TBM) is the most common form of central nervous system tuberculosis with a very poor prognosis. We aimed at assessing risk factors related to the prognosis of patients with TBM.

Forty-five inpatients with TBM in our institution from January 2013 to December 2015 were enrolled retrospectively. The good or poor prognosis in the patients was defined, based on Glasgow Outcome Scale System at discharge. Patients with a GOS score less than 5 were defined as "poor prognosis." Univariate and multivariate logistic regression analyses were performed to assess the predictors for TBM outcome.

Among 45 TBM patients, 35 (77.8%) and 10 (22.2%) were in good, poor prognoses, respectively. Old age, disturbance of consciousness, moderate to severe electroencephalogram abnormality, hydrocephalus, remarkable increase of protein (≥ 236 mg/dL) and white blood cell counts (≥ 243/μL) in cerebral spinal fluid were associated with poor prognosis. Multivariate analysis indicated that old age (odds ratio (OR) = 18.395, $P = .036$) and hydrocephalus (OR = 32.995, $P = .049$) were independent factors for a poor outcome of TBM.

In conclusion, old age and hydrocephalus are the predictors for poor prognosis of TBM. Patients with these risk factors should be treated promptly with a special care paid to improve their outcomes.

Abbreviations: ADA = adenosine deaminase, AIDS = acquired immune deficiency syndrome, CNS = central nervous system, CSF = cerebral spinal fluid, CT = computed tomographies, DALYs = disability-adjusted life years, EEG = electroencephalogram, GOS = Glasgow Outcome Scale, MRI = magnetic resonance imaging, OR = odds ratio, SD = standard deviation, TB = tuberculosis, TBM = tuberculous meningitis, V-P shunt = ventriculo-peritoneal shunt, WBC = white blood cells.

Keywords: logistic regression analysis, predictors, prognosis, tuberculous meningitis

1. Introduction

Tuberculosis (TB) is a major global health burden. In 2012, TB killed 1.3 million people worldwide.[1] In 2013, there were approximately 11 million prevalent TB cases worldwide.[2] Tuberculous meningitis (TBM) is the infection of the meninges by *Mycobacterium tuberculosis*. The infection site locates at the membranes which envelop the central nervous system (CNS). It is a very severe form of tuberculosis in terms of permanent sequelae and fatal ending.[3–5] It is commonly known that TBM carries a high morbidity and mortality.[6–8] In addition, serious neurological deficits such as cognitive impairment, hemiplegia, seizures, quadriplegia, and cranial nerve palsy commonly happened in TBM survivors.[5] Hence, a better understanding of the prognostic factors for TBM is essential for improving the life quality of patients.

Previous data have indicated that early diagnosis and in-time treatment is the most important issue related to the complications and mortality rates of TBM.[9–11] Nevertheless, with the advancement in molecular diagnosis, imaging techniques and newly developing anti-tuberculous (anti-TB) agents, recent studies related to TBM prognostic factors are still absent. In this study, we analyzed the risk factors associated with TBM prognosis, and planned to find out predictors for poor outcomes of TBM.

2. Methods

2.1. Patients and diagnosis of TBM

It was a retrospectively observational study, which enrolled consecutive patients with TBM admitted to Zhejiang Provincial People's Hospital from January, 2013 to December, 2015. The

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H-JH, Z-ZR, and Y-ND contributed equally to this work.

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study protocol complied with the ethical guidelines of the Declaration of Helsinki. Written informed consents were waived as we used only data routinely collected during hospitalization.

The inclusion criteria were based on the following diagnostic standards of TBM[12,13]: symptoms and clinical signs of meningitis, for example, headache, fever, vomiting, photophobia, irritability, neck stiffness, focal neurological deficits, convulsions, altered consciousness, or lethargy; finding of active or previous extra-CNS tuberculosis infection; acid-fast bacilli seen in the cerebral spinal fluid (CSF); *Mycobacterium tuberculosis* cultured from the CSF; typical changes of CSF, including pleocytosis (>20 cells/μL), lymphocytes >60%, protein >1 g/L, and CSF to blood glucose ratio of <0.6; recall of recent exposure to tuberculosis; response to antituberculosis therapy. Criterion 1, 5, and 7 were necessary to define a case, while the other items were dispensable (at least 1 of them should be met). The diagnosis of TBM and the inclusion of each subject were approved by at least 2 experienced physicians in the Department of Infectious Disease, Zhejiang Provincial People's Hospital. Children and adolescents whose ages were less than 18 years should be excluded.

2.2. Collection of clinical data

Data related to age, gender, comorbidities, clinical manifestations, treatment, and duration from onset to admission were collected. In addition, routine and biochemical analysis of CSF on admission were recorded, such as CSF pressure (in mm H_2O), white blood cells (WBC) counts (/uL), glucose (in mmol/L), protein (in mg/dL), chloride (in mmol/L), and adenosine deaminase (ADA) (in U/L). Furthermore, chest computed tomography (CT), electroencephalogram (EEG), brain CT or magnetic resonance imaging (MRI) were performed on every patient after admission, and the corresponding imaging data were documented. Hydrocephalus was diagnosed according to the results of brain CT or MRI.

2.3. Assessment of disease prognosis

Prognosis was determined prior to discharge using the Glasgow Outcome Scale (GOS).[14] The GOS consists of 5 categories: patients would get 5 scores when they were in good recovery; those who were moderately disabled but still independent would be scored 4; subjects with severe disability but still conscious could reached to 3 scores; patients with vegetable state would be scored 2; dead patients would be scored 1. Disease prognosis was assessed independently by 2 investigators, and disagreements would be solved by a discussion.

All the patients were distributed into 2 groups: those with a GOS score of 5 were considered as "good prognosis," while patients scored from 1 to 4 were allocated into the "poor prognosis" group.

2.4. Statistical analysis

All statistical analyses were performed using SPSS software (version 21.0). Categorical data were expressed as number (percentage) while measurement data were presented in the form of both "mean ± standard deviation" and "median (range)." The Student *t* test or χ^2 test was used for the comparison between groups with good and poor prognosis. Univariate and multivariate binary logistic regression analyses were conducted to evaluate risk factors associated with the prognosis of TBM. A *P* value of less than.05 was considered to be statistically significant.

Table 1

Baseline characteristics of patients with TBM.

Characteristics	Value*
Gender (male/female)	30/15
Age	46.04 ± 17.01/45 (20–85)
Comorbidities	
Extra-CNS TB	29 (64.4%)
Active extra-CNS TB	5 (11.1%)
AIDS	6 (13.3%)
Diabetes mellitus	4 (8.9%)
Recent contact with TB	7 (15.6%)
Symptoms	
Fever	45 (100%)
Headache	29 (64.4%)
Nausea and vomiting	27 (60%)
Disturbance of consciousness	11 (24.4%)
Clinical signs	
Neck stiffness	39 (86.7%)
Kernig sign	18 (40%)
Brudzinski sign	18 (40%)
Babinski sign	15 (33.3%)
Cranial nerve lesions	15 (33.3%)
CSF parameters	
Pressure, mm H_2O	232.07 ± 85.66/210 (100–400)
WBC counts, /uL	243.78 ± 182.41/190 (39–830)
ADA, U/L	6.67 ± 5.32/6 (1–26)
Protein, mg/dL	236.54 ± 133.74/216.8 (80.2–830)
Glucose, mmol/L	1.99 ± 0.69/1.8 (0.6–3.4)
Chloride, mmol/L	110.69 ± 5.30/111 (100.4–118.4)
EEG	
Mild abnormal	29 (64.4%)
Moderate to severe abnormal	16 (35.6%)
Hydrocephalus	6 (13.3%)
Treatment	
Antibiotics†	23 (51.1%)
Corticosteroids	16 (35.6%)
V-P shunt or CSF drainage	3 (6.7%)
GOS	
5	35 (77.8%)
4	7 (15.6%)
3	2 (4.5%)
2	0
1	1 (2.2%)

ADA = adenosine deaminase, AIDS = acquired immune deficiency syndrome, CSF = cerebral spinal fluid, EEG = electroencephalogram, Extra-CNS TB = extra-central nervous system tuberculosis, GOS = Glasgow Outcome Scale, TBM = tuberculous meningitis, V-P shunt = Ventriculo-peritoneal-shunt, WBC = white blood cell.

* Categorical data were expressed as number (percentage), and measurement data were presented in the form of both "mean ± standard deviation " and "median (range)."

† Antibiotics refer to antibiotics other than antituberculosis drugs.

3. Results

3.1. Baseline characteristics

A total of 45 patients were included in this study. The clinical characteristics of the subjects are exhibited in Table 1. There were 30 males and 15 females, whose age ranged from 20 to 85 years. Twenty-nine patients were identified as extra-CNS tuberculosis, while 6 patients combined with Acquired Immune Deficiency Syndrome (AIDS). In this study, all 45 patients presented fever, while a proportion of subjects exhibited other different clinical symptoms, for example headache, nausea and vomiting, and disturbance of consciousness. Hydrocephalus was diagnosed in 6 patients through brain CT or MRI, and 3 of them received surgical intervention like ventriculo-peritoneal (V-P) shunt of CSF drainage. While hospitalized, 23 cases received antibiotics (except

Table 2

Univariate analysis of prognostic factors associated with TBM.

Risk factors	Good prognosis (n = 35)	Poor prognosis (n = 10)	*P* value
Duration from onset to admission			
>1 mo	6 (17.1%)	5 (50%)	.086
1 wk to 1 mo	23 (65.7%)	3 (30%)	.098
<1 wk	6 (17.1%)	2 (20%)	1.000
Gender			
Male	25 (71.4%)	5 (70%)	.375
Female	10 (28.6%)	5 (30%)	
Age (mean ± SD)	41.86 ± 14.63	60.70 ± 17.28	.001
median (range)	42 (20–70)	61.5 (46–85)	
Comorbidities			
Extra-CNS TB	22 (62.9%)	7 (70%)	.967
AIDS	4 (11.4%)	2 (20%)	.860
Diabetes mellitus	2 (5.7%)	2 (20%)	.441
Fever			
Body temperature > 39°C	8 (22.9%)	5 (50%)	.202
Body temperature < 39°C	27 (77.1%)	5 (50%)	
Headache	23 (65.7%)	6 (60%)	1.000
Nausea and vomiting	20 (57.1%)	7 (70%)	.714
Disturbance of consciousness	5 (14.3%)	6 (60%)	.011
Neck stiffness	31 (88.6%)	8 (80%)	.860
Kernig sign	11 (31.4%)	7 (70%)	.067
Brudzinski sign	12 (34.3%)	6 (60%)	.272
Babinski sign	9 (25.7%)	6 (60%)	.099
Cranial nerve lesions	10 (28.6%)	5 (50%)	.375
CSF pressure, mm H_2O			
>230	17 (48.6%)	3 (30%)	.496
180–230	6 (17.1%)	3 (30%)	.654
<180	12 (34.3%)	4 (40%)	1.000
CSF protein, mg/dL			
≥236	13 (37.1%)	9 (90%)	.010
<236	22 (62.9%)	1 (10%)	
CSF glucose, mmol/L			
2–2.5	2 (5.7%)	1 (10%)	.714
<2	17 (57.1%)	7 (70%)	
CSF chloride, mmol/L			
≥110	22 (62.9%)	8 (80%)	.526
<110	13 (37.1%)	2 (20%)	
CSF WBC counts (/uL)			
≥243	9 (25.7%)	7 (70%)	.027
<243	26 (74.3%)	3 (30%)	
ADA, U/L			
≥6.67	12 (34.3%)	7 (70%)	.098
<6.67	23 (65.7%)	3 (30%)	
Moderate to severe abnormality of EEG	9 (25.7%)	7 (70%)	.027
Hydrocephalus	2 (5.7%)	4 (40%)	.022
Treatment			
Antibiotics*	16 (45.7%)	7 (70%)	.319
Corticosteroids	10 (28.6%)	6 (60%)	.145

ADA = adenosine deaminase, AIDS = acquired immune deficiency syndrome, CSF = cerebral spinal fluid, EEG = electroencephalogram, Extra-CNS TB = extra-central nervous system tuberculosis, SD = standard deviation, TBM = tuberculous meningitis, WBC = white blood cell.

* Antibiotics refer to antibiotics other than antituberculosis drugs.

for antituberculosis drugs) to prevention and cure secondary infections. All patients received tuberculostatic therapy, while 16 cases have been given corticosteroids during their hospitalization.

On discharge, 35 of the patients attained a good recovery, with a GOS score of 5 on discharge. Meanwhile, 7 cases got a GOS score of 4, and 2 subjects were scored 3. Varying degrees of cognitive impairment and limb paralysis were the common neurologic sequelae happened in these patients. Unfortunately, one patient was dead in the end (GOS 1).

Table 3

Independent prognostic factors associated with TBM.

Variables	β	SE	OR	*P* value
Age	2.912	1.390	18.395	.036
Disturbance of consciousness	0.512	1.492	1.669	.731
CSF protein ≥ 236 mg/dL	3.214	1.687	0.040	.057
CSF WBC counts ≥ 243 /uL	0.700	1.557	0.497	.653
Moderate to severe abnormality of EEG	0.335	1.226	1.398	.785
Hydrocephalus	3.496	1.775	32.995	.049

β = regression coefficient, CSF = cerebral spinal fluid, EEG = electroencephalogram, OR = odds ratio, SE = standard error, WBC = white blood cell.

3.2. Predictive factors of TBM prognosis

The 35 patients with a GOS score of 5 were distributed into the "good prognosis" group, whereas the other 10 patients (22.2%) with a GOS score less than 5 were classified into the "poor prognosis" group. Univariate analysis indicated that old age ($P = .001$), disturbance of consciousness ($P = .011$), moderate to severe abnormality of EEG ($P = .027$), hydrocephalus ($P = .022$), increased CSF protein levels (≥ 236 mg/dL) ($P = .010$), and increased CSF WBC counts (≥ 243/μL) ($P = .027$) were associated with worse prognosis of TBM (Table 2). The application of corticosteroid seemed not to improve the outcome.

In the subsequent multivariate analysis, old age (OR = 18.395, $P = .036$) and hydrocephalus (OR = 32.995, $P = .049$) were observed to be independently associated with a poor outcome of TBM (Table 3). Increased level of CSF proteins seemed to be related to unfavorable prognosis (OR = 0.040), but the *P* value ($P = .057$) indicated only borderline significance. However, there were no statistical associations between the prognosis of TBM with the other risk factors, for example the disturbance of consciousness, abnormality of EEG, and increased CSF WBC counts.

4. Discussion

At the present time, TB is still a serious health burden worldwide, especially in less-developed regions.[15] The development of drug-resistant *Mycobacterium tuberculosis* and the AIDS epidemic particularly contribute to the increased prevalence of TB. Based on the 2010 disability-adjusted life years (DALYs) proposed by the Global Burden of Disease Study, TB is the 10th factor causing death, and the 13th factor of disability.[16] Despite the availability of effective chemotherapy, TB remains one of the top causes of death from infectious disease.[1]

TBM is a very critical form of TB, and is often recognized as a medical emergency. Immune-suppressed patients, especially those with human immunodeficiency virus infection, are more likely to suffer disseminated TB with CNS involvement.[17] However, the diagnosis of TBM is often obscured because of its nonspecific symptoms.[18] Thus, treatment is delayed, leading to a poor outcome. Understanding the risk factors related to the prognosis may improve its outcome. In this study, we investigated potential prognostic factors of TBM, in the purpose of timely intervention and offering more realistic expectations for patients and their relatives.

In fact, a considerable number of studies have found numerous factors related to the outcome of TBM. Except for the prompt identification of disease and early anti-TB therapy,[11,19] advanced age, altered consciousness, presence of seizures, immunosuppression, diabetes mellitus, vasculitis, positive TB culture, or polymerase chain reaction of CSF and hydrocephalus

have been reported to predict the unfavorable outcome.[20–23] In addition, prognostic factors of neurological sequelae in patients with TBM include tuberculoma, focal neurological signs, and cranial nerve palsy.[5,22,24] However, in recent years, the predictors of TBM might change with the development in diagnostic techniques and the accessibility of effective chemotherapy. Reviewing the published literatures, recent prognostic analyses of TBM are relatively absent, especially in China. One research by Gu et al[25] published in 2015 has indicated that advanced age, changes in consciousness, low Glasgow coma scale (GCS) score on admission and concomitant hydrocephalus are independent risk factors of TBM. But the study region is localized at Shanghai. Therefore, we performed a retrospective observational study in Hangzhou to identify predictors of TBM in a Chinese adult population.

In this study, the age of patients with favorable prognosis was 41.86 ± 14.63, significantly younger than patients with poor outcomes (mean age 60.70 ± 17.28). Cases with good outcomes had lower levels of CSF protein, WBC counts than cases with poor prognosis. Moreover, disturbance of consciousness, hydrocephalus, and moderate to severe abnormality of EEG were more prevalent in cases with unfavorable outcomes. Further multivariate analysis has demonstrated that old age and hydrocephalus are independent risk factors associated with the prognosis of TBM. Hence, we see that the results of this study agreed with the findings of previous studies.

Hydrocephalus is a quite common complication of TBM.[26] Communicating hydrocephalus develops because of either overproduction of CSF or malfunctioning absorption of CSF in the subarachnoid space. Besides, the obstructive type of hydrocephalus is less common, which develops on account of the obstruction of the fourth ventricular outlets by inflammatory exudate. We believed that hydrocephalus in TBM carried a higher risk of poor prognosis. Therefore, the management of hydrocephalus is an essential issue. Mild hydrocephalus responds to medical therapy, whereas surgery should be required in case of raised intracranial pressure.[26] However, the indications for V-P shunt, or CSF drainage is debatable, and the curative effect of surgical interventions remains controversial.[27–29] Additional robust research exploring the optimal management for hydrocephalus in TBM is needed.

The limitation of this study was the relatively small sample size. Because it was based on a single-center infirmary, only 45 subjects were included. This might affect the stability of logistic model. Further multicenter large-scale prognostic studies in China are necessary for the better guidance of clinical decision making in TBM.

In conclusion, the study has found that TBM patients with advanced age and hydrocephalus had higher odds of a poor outcome. In clinical practice, physicians should pay more attention to those patients with old age or hydrocephalus.

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