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Original Article

Prognostic Factors of Tuberculous Meningitis in Adults: A 6-Year Retrospective Study at a Tertiary Hospital in Northern Taiwan

Po-Chang Hsu, Chien-Chang Yang, Jung-Jr Ye, Po-Yen Huang, Ping-Cherng Chiang, Ming-Hsun Lee*

Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan.

BACKGROUND/PURPOSE: To investigate the clinical features, laboratory test results, imaging data, and prognostic predictors of tuberculous meningitis (TBM) in adults.

METHODS: We retrospectively reviewed 108 adult patients with a diagnosis of TBM over a 6-year period. Patients were divided into "definite" and "probable" groups, depending on the diagnosis made by (1) positive culture, or polymerase chain reaction, of *Mycobacterium tuberculosis* (TB) from the cerebrospinal fluid (CSF); or (2) the isolation of TB elsewhere, or chest radiography consistent with active pulmonary TB, or imaging studies of the brain consistent with TBM, or clinical improvement on treatment. These two groups were compared for their clinical features, images, laboratory test results, and 9-month mortality rates to identify prognostic predictors.

RESULTS: Compared with the "probable" group ($n=62$), the "definite" group ($n=46$) had a higher mortality rate (50.0% *vs.* 30.6%, $p=0.041$) and more consciousness disturbance (78.3% *vs.* 51.6%, $p=0.005$), hydrocephalus (63.4% *vs.* 40.7%, $p=0.029$) and isolation of TB from extra-CSF specimens (41.3% *vs.* 22.6%, $p=0.037$). Old age ($p=0.002$), consciousness change ($p=0.032$), and hydrocephalus ($p=0.047$) were poor prognostic indicators in the "definite" group as assessed by univariate analysis. Severity of TBM at admission and delayed anti-TB therapy resulted in a poor prognosis for all patients. Multiple logistic regression analysis showed that old age and hydrocephalus were independent factors for mortality. Adjunctive steroid therapy over 2 weeks improved survival in both the "definite" ($p=0.002$) and "probable" ($p=0.035$) groups, but more than 4 weeks of use had no significant effect on mortality. Steroid treatment, therefore, may improve the outcome of patients with TBM.

*Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital, 5 Fu-Shin Street, Gueishan 333, Taoyuan, Taiwan.

E-mail: drharrylee@gmail.com

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CONCLUSION: Old age, advanced stage of TBM at admission, hydrocephalus, and positive TB culture or polymerase chain reaction of CSF are factors associated with a poor prognosis for TBM. Early diagnosis and treatment, including short term steroid use, are mandatory for clinical care of adult patients with TBM.

KEYWORDS: hydrocephalus, prognostic factors, steroid, tuberculous meningitis

Introduction

Mycobacterium tuberculosis remains a global epidemic, especially in Asia. In 2006, 9.2 million new cases and 1.7 million deaths from tuberculosis (TB) occurred, of which 0.7 million cases and 0.2 million deaths were in HIV-positive people.[1] *M. tuberculosis* infection is still an important public health issue worldwide. Tuberculous meningitis (TBM) is a major cause of this serious illness in many parts of the world, especially in developing countries.[2] The mortality rate for TBM is around 20–41%.[2–4] Many prognostic factors for TBM have been reported, including age, the stage of the disease, level of consciousness, presence of extra-central nervous system (CNS) TB, isolation of *M. tuberculosis* from cerebrospinal fluid (CSF), biochemical studies of CSF, hydrocephalus, and infarction.[5–7] Even so, early diagnosis and treatment of the disease is the most important factor affecting complications and mortality rates.[6,8,9] However, it is still difficult, using the current parameters, to make an early and precise diagnosis on the basis of laboratory results.[10]

TBM still causes death, or severe neurologic deficits, despite the advent of newer antituberculous (anti-TB) agents and imaging techniques. Recently, some studies have reported that, adjunctive steroids might be of benefit to patients with TBM.[11,12]

Hydrocephalus is a frequent complication of TBM and, as yet, the best way to manage this has still to be found. The emergence of drug-resistant strains has increased in many parts of the world and this disease presents a therapeutic challenge.[13] Thus, to identify prognostic predictors for TBM, we conducted a retrospective study at a tertiary teaching hospital over a 6-year period in which we evaluated clinical outcomes, laboratory data, neuroimaging results, and therapeutic factors associated with mortality in patients with a diagnosis of TBM.

Methods

Patients and study design

Data obtained from patients (aged ≥ 16 years) admitted to the Chang Gung Memorial Hospital-Linkou Medical Center between January 2000 and September 2006 with a diagnosis of TBM was analyzed retrospectively. The patients' medical records were reviewed, and the following information was collected: demographic characteristics, underlying diseases, clinical features, laboratory data, bacteriology, image studies, use of steroids, mannitol and anti-TB agents, surgical interventions or drainage, and clinical outcome. Most patients had CSF taken on admission, and the following tests performed: total cell count, glucose, protein and lactate levels, polymerase chain reaction for TB (TB-PCR), and mycobacterial smears and cultures. We also collected follow-up CSF data, if available. Chest radiography was performed on all patients on admission, and brain computed tomography (CT) scans or magnetic resonance imaging (MRI) studies were done for most patients after admission. Findings consistent with TBM in the brain CT or MRI scans were as follows: exudates in the basal cisterns, hydrocephalus, gyral enhancement, tuberculoma, vasculitis, and abscess or infarcts.

The diagnosis of TBM was based on clinical features, routine CSF screens, biochemistry, microbiologic cultures, and brain imaging results.[14] Clinical features included fever for more than 7 days, headache, or neck stiffness. Patients were classified into one of two groups; "definite" or "probable", to assess differences in mortality and clinical severity. "Definite" TBM was defined as the isolation of *M. tuberculosis* from one or more CSF cultures, and/or positive TB-PCR. "Probable" TBM was defined as the presence of CSF findings compatible with TBM, i.e., CSF leukocyte count > 10/μL (with a predominance of lymphocytes), protein > 40 mg/dL, low CSF/serum

glucose ratios (< 0.6), or < 60 mg/dL, plus one or more of the following criteria: (1) isolation of *M. tuberculosis* from specimens other than the CSF, or findings of active pulmonary TB on chest radiography; (2) radiological findings on cranial CT or MRI consistent with TBM; (3) a history of TB infection; and (4) clinical improvement after anti-TB treatment.[2,9] Patients were excluded from the statistics if they had any evidence of CNS malignancy ($n = 3$), or were lost to follow-up ($n = 9$) during, or after, the period of anti-TB treatment. The duration of loss of follow-up was 6 days to 5 months (mean, 3.7 months).

The severity of TBM at the time of admission was assessed using the British Medical Research Council TBM grades.[15] Grade I is defined as a Glasgow coma score (GCS) of 15 without focal neurological signs; grade II is defined as a GCS of 15 with neurological deficit, or a GCS of 11–14; and grade III is defined as a GCS of ≤ 10.

Treatment

Patients received a minimum of two bactericidal anti-TB agents such as isoniazid (INH) 300 mg/day, rifampicin (RIF) 450–600 mg/day, or pyrazinamide 1000–1500 mg/day, either with or without ethambutol 800–1200 mg/day, for at least 6 months—unless the patient died. Other anti-TB agents such as ciprofloxacin 1 g/day, levofloxacin 500 mg/day, or streptomycin 15 mg/kg/day, were used temporarily in patients who experienced drug toxicity. The time between the onset of presenting clinical features and the start of anti-TB therapy was recorded. Adjunctive steroid therapy was defined as the use of prednisolone ≥ 20 mg/day for at least 7 consecutive days, and the treatment duration was categorized as over 7 days, 14 days, 21 days, and 28 days. Hydrocephalus was treated with steroids, mannitol, or surgical intervention. The outcome was assessed in terms of survival after 9 months from entry (9-month mortality).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables as a proportion of the total number of patients. Univariate analysis was conducted using either a χ^2 test, or Fisher's exact test for categorical variables, and Student's *t* test, or Mann-Whitney *U* test, for continuous variables, as indicated. The relationship between mortality and disease stage was evaluated using logistic regression analysis. To eliminate confounding factors in predicting the risk for mortality, variables with *p* values ≤ 0.1 by univariate analysis were entered into a multivariate logistic regression model for further assessment. All statistical calculations were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Results were expressed as adjusted odds ratios, and corresponding 95% confidential interval (CI). A *p* value of < 0.05 was regarded as significant.

Results

A total of 108 patients were included in this study. Their demographic and clinical features, along with laboratory data are summarized in Table 1. Of the 108 patients, 71 (65.7%) were male. The mean age of the patients was 54.9 ± 18.6 years (range, 19–87 years). The common presenting symptoms and signs were as follows: fever (81.5%), consciousness disturbance (63.0%), headache (60.2%), neck stiffness (54.6%), vomiting (20.3%), seizure (13.9%), unstable gait (7.4%), double vision (5.6%), photophobia (2.7%), urinary incontinence (2.7%), hemiplegia (1.8%), and deafness (0.9%). On admission, 24 patients (22.2%) were classified as stage I, 56 (51.9%) as stage II, and 28 (25.9%) as stage III. Isolation of *M. tuberculosis* from specimens other than the CSF was positive in 33 patients. These included sputum or bronchial alveolar lavage samples (26 patients), muscle abscess (1 patient), urine (1 patient), and simultaneous multiple sites (5 patients). The simultaneous multiple sites included sputum and spinal tissue (2 patients); sputum and urine (1 patient); sputum and ascites (1 patient); sputum, lymph node, pericardium and spinal tissue (1 patient).

Of the 108 patients, one had a positive CSF smear for acid fast stain, with both positive culture and PCR. PCR for the specific detection of *M. tuberculosis* was carried out in 49 cases, 15 (30.6%) of which were positive. Forty-two patients (38.9%) had *M. tuberculosis* isolated from CSF specimens, and six of the isolates (14.6%) were resistant strains; two INH-resistant strains, one RIF-resistant strain, one pyrazinamide-resistant strain, one streptomycin-resistant strain, and one multiple-drug (INH, RIF and ethambutol) resistant strain.

Routine CSF results were as follows: leukocyte count, 220.4 ± 312.7/μL; protein levels, 316.2 ± 434.6 mg/dL;

Table 1. Demographic and clinical characteristics in patients with tuberculous meningitis[a]

Characteristics	"Definite" patients (n=46)	"Probable" patients (n=62)	Total patients (n=108)	Univariate p[b]
Age (yr)	56.7±19.2	53.7±18.2	54.9±18.6	0.395
Gender, male	27 (58.7)	43 (69.4)	71 (65.7)	0.251
Presentations				
Fever (>38°C)	37 (80.4)	51 (82.3)	88 (81.5)	0.809
Conscious disturbance	36 (78.3)	32 (51.6)	68 (63.0)	0.005
Headache	25 (54.3)	40 (64.5)	65 (60.2)	0.214
Neck stiffness	21 (45.7)	38 (61.3)	59 (54.6)	0.106
Tuberculosis other than CNS	19 (41.3)	14 (22.6)	33 (30.6)	0.037
Stage of TBM at admission				
Stage I	5 (10.9)	19 (30.6)	24 (22.2)	0.015
Stage II	24 (52.2)	32 (51.6)	56 (51.9)	
Stage III	17 (37.0)	11 (17.7)	28 (25.9)	
CSF routine				
WBC (/μL)	221.8±306.5	219.5±319.5	220.4±312.7	0.693
Protein (mg/dL)	346.3±548.1	293.7±334.2	316.2±434.6	0.250
Glucose (mg/dL)	42.4±34.4	46.6±28.8	44.8±31.1	0.092
Lactate (mg/dL)	62.2±23.7	46.9±21.1	53.0±23.3	0.002
Image[c]				
Hydrocephalus	26 (63.4)	22 (40.7)	48 (50.5)	0.029
Meningitis sign[d]	11 (26.8)	18 (33.3)	29 (30.5)	0.495
Infarction	9 (22.0)	13 (24.1)	22 (23.2)	0.808
Mortality	23 (50.0)	19 (30.6)	42 (38.9)	0.041
Duration between admission and death (d)	61.1±70.9 (5–232)	67.03±52.1 (5–205)	63.8±62.4 (5–232)	0.097

[a]Data presented as n (%), mean±standard deviation or mean±standard deviation (range); [b]comparison between "definite" group and "probable" group; [c]95 patients had imaging data, of them 41 were in "definite", 54 in "probable"; [d]exudates in basal cisterns, hydrocephalus, gyral enhancement, tuberculoma, vasculitis, abscess, or infarcts. CNS=Central nervous system; TBM=tuberculous meningitis; CSF=cerebrospinal fluid; WBC=white blood cells.

glucose levels, 44.8±31.1 mg/dL; and lactate levels, 53.0±23.3 mg/dL.

Ninety-five patients had brain CT or MRI scans during their hospital stay. Twenty-four patients had negative findings. Positive image findings were as follows: hydrocephalus (48 patients, 50.5%), meningitis signs (29 patients, 30.5%; with leptomeningeal enhancement in 12 patients, basal cisterns enhancement in 9 patients, frontotemporal enhancement in 3 patients, granulomatous enhancement in 1 patient, tentorium and sulci fissure enhancement in 1 patient and radiologist-suspected meningitis in 3 patients), infarction (22 patients, 23.2%), abscess (4 patients, 4.2%), tuberculoma (4 patients, 4.2%), and vasculitis (2 patients, 2.1%). Forty-two patients (38.9%) died within 9 months. The mean time of death was 63.8±62.4 days (range, 5–232 days), with 75% dying within 90 days.

Forty-six patients were assigned to the "definite" group. Twenty-three patients (50%) in the "definite" group, and 19 patients (30.6%) in the "probable" group, died. The "definite" group had a higher mortality rate (p=0.041), and patients had more advanced disease on admission compared with the "probable" group (p=0.015). However, the mean number of days between admission and death was not significantly different between the two

Table 2. Prognostic factors in patients with tuberculous meningitis[a]

Variables	"Definite" patients (n=46)			"Probable" patients (n=62)			Total patients (n=108)		
	Deceased (n=23)	Survived (n=23)	Univariate p	Deceased (n=19)	Survived (n=43)	Univariate p	Deceased (n=42)	Survived (n=66)	Univariate p
Mean age (yr)	64.6	48.6	0.002	66.6	48.0	<0.001	65.5	48.2	<0.001
Age > 60	15 (65.2)	7 (30.4)	0.018	13 (68.4)	12 (27.9)	0.003	28 (66.7)	19 (28.8)	<0.001
Gender, male	16 (69.6)	11 (47.8)	0.134	10 (52.6)	33 (76.7)	0.058	26 (61.9)	44 (66.7)	0.613
TB other than CNS	12 (52.2)	7 (30.4)	0.134	5 (26.3)	9 (20.9)	0.744	17 (40.5)	16 (24.2)	0.074
Presentations									
Fever	20 (87.0)	17 (73.9)	0.265	14 (22.6)	37 (59.7)	0.240	34 (31.5)	54 (50.0)	0.910
Headache	11 (47.8)	14 (60.9)	0.375	11 (57.9)	30 (69.8)	0.362	22 (52.4)	44 (66.7)	0.138
Conscious change	21 (91.3)	15 (65.2)	0.032	12 (63.2)	20 (46.5)	0.227	33 (78.6)	35 (53.0)	0.007
Neck stiffness	10 (43.5)	11 (47.8)	0.767	9 (47.4)	29 (67.4)	0.135	19 (45.2)	40 (60.6)	0.118
CSF routine									
WBC (/μL)	140.0	116.5	0.544	49.0	145.0	0.002	97.0	135.0	0.084
Protein (mg/dL)	259.0	211.6	0.680	187.0	200.2	0.434	237.7	208.3	0.312
Glucose (mg/dL)	33.0	30.0	0.697	44.5	40.0	0.591	41.5	36.5	0.764
Lactate (mg/dL)	60.0	59.6	0.457	53.7	40.9	0.449	58.1	54.0	0.110
Stage of TBM at admission									
Stage I	2 (8.7)	3 (13.0)	0.101	5 (26.3)	14 (32.6)	0.165	7 (16.7)	17 (25.8)	0.006
Stage II	9 (39.1)	15 (65.2)		8 (42.1)	24 (55.8)		17 (40.5)	39 (59.1)	
Stage III	12 (52.2)	5 (21.7)		6 (31.6)	5 (11.6)		18 (42.9)	10 (15.2)	
Timing of starting anti-TB[b] (d)	15.9	12.6	0.176	20.6	12.5	0.127	18.2	12.6	0.044
Steroid									
>1week	8 (34.8)	14 (60.9)	0.077	4 (21.1)	20 (46.5)	0.058	12 (28.6)	34 (51.5)	0.019
>2 weeks	1 (4.3)	10 (43.5)	0.002	2 (10.5)	17 (39.5)	0.035	3 (7.1)	27 (40.9)	<0.001
>3 weeks	1 (4.3)	9 (39.1)	0.004	1 (5.3)	9 (20.9)	0.155	2 (4.8)	18 (27.3)	0.003
>4 weeks	1 (4.3)	4 (17.4)	0.346	1 (5.3)	4 (9.3)	1.000	2 (4.8)	8 (12.1)	0.310
Mannitol	8 (34.8)	8 (34.8)	1.000	5 (26.3)	14 (32.6)	0.623	13 (31.0)	22 (33.3)	0.797
Image	(n=22)	(n=19)		(n=18)	(n=36)		(n=40)	(n=55)	
Hydrocephalus	17 (77.3)	9 (47.4)	0.047	13 (72.2)	9 (25.07)	0.001	30 (75.0)	18 (32.7)	<0.001
Infarction	7 (31.8)	2 (10.5)	0.140	4 (22.2)	9 (25.0)	0.882	11 (27.5)	11 (20.0)	0.392
Meningitis sign	4 (18.2)	7 (36.8)	0.179	7 (38.9)	11 (30.6)	0.540	11 (27.5)	18 (32.7)	0.586

[a]Data presented as n (%) or mean; [b]duration between the onset of presenting clinical features and the start of antituberculous therapy. TB=Tuberculosis; CNS=central nervous system; CSF=cerebrospinal fluid; WBC=white blood cells; TBM=tuberculous meningitis.

groups (61.1±70.9 *vs.* 67.03±52.1, p=0.097). Moreover, consciousness disturbance, hydrocephalus, and a higher rate of extra-CNS TB were more common in the "definite" group, 78.3% *vs.* 51.6%, (p=0.005); 63.4% *vs.* 40.7%, (p=0.029); and 41.3% *vs.* 22.6%, (p=0.037), respectively.

In the "definite" group, univariate analysis revealed that both old age (p=0.002) and consciousness disturbance (p=0.032) were associated with a higher mortality (Table 2). As for the image findings, hydrocephalus was the most frequent finding and was obviously correlated

with mortality ($p=0.047$), and adjunctive steroid therapy over 2 or 3 weeks was associated with a significantly reduced risk of death. The deceased patients had experienced greater delays in the administration of anti-TB agents than those that survived (15.9±9.1 *vs.* 12.6±7.3 days), but this difference was not significant ($p=0.176$). Age and hydrocephalus were also significantly associated with higher mortality in the "probable" group, $p<0.001$ and $p=0.001$, respectively, and adjunctive steroid use over 2 weeks significantly reduced the mortality rate ($p=0.035$). Overall, the CSF white cell count was lower in those patients that survived than in those that did not ($p=0.002$).

The potential risk factors for mortality in all patients are listed in Table 2. Statistically significant factors were: age over 60 years ($p<0.001$), consciousness disturbance ($p=0.007$), and hydrocephalus ($p<0.001$). The staging of TBM at admission was associated with increased mortality in all patients ($p=0.006$). Logistic regression analysis showed that, for all patients, there was no statistical difference in mortality between TBM stage I and stage II ($p=0.915$; 95% CI=0.371–3.020), but patients with TBM stage III had a higher mortality rates compared with those with TBM stage I ($p=0.014$; 95% CI=1.355–14.10). In this case, the deceased patients had experienced significant delays in the administration of anti-TB agents compared with those that survived (18.2±12.6 *vs.* 12.6±6.3 days; $p=0.044$). Those patients treated with steroids over one, 2 or 3 weeks had a lower mortality rate ($p=0.019$, $p<0.001$, and $p=0.003$, respectively), but this was not statistically significant in patients treated over 4 weeks ($p=0.310$). Variables used in the multivariate logistic regression included age, CSF white cell counts, isolation of *M. tuberculosis* or positive TB-PCR in CSF, stage of TBM, the timing anti-TB therapy administration, steroid treatment over 2 weeks, extra-CNS TB, and hydrocephalus (Table 3). The results show that age ($p=0.041$), hydrocephalus ($p=0.016$), and delays in starting anti-TB therapy and steroids ($p=0.001$) were independently associated with increased mortality. Forty-eight patients had hydrocephalus, and steroid treatment improved the outcome in these patients by reducing the mortality rate in this group ($p<0.001$). Ventriculoperitoneal (V-P) shunt/CSF drainage and mannitol treatment did not improve the mortality rates ($p=0.450$ and $p=0.499$, respectively).

Table 3. Multivariate logistic regression model showing the parameters for the mortality of tuberculous meningitis

Risk factor	Odds ratio (95% CI)	*p*
Age	1.046 (1.002–1.091)	0.041
Isolation of TB or positive TB-PCR in CSF	1.153 (0.302–4.406)	0.835
Tuberculosis other than CNS	1.168 (0.246–5.554)	0.845
CSF WBC	1.001 (0.999–1.003)	0.547
Conscious change	1.675 (0.207–13.572)	0.629
Stage of TBM		
II *vs.* I	0.455 (0.052–3.985)	0.477
III *vs.* I	1.945 (0.141–26.912)	0.620
Timing of starting anti-TB[a]	1.082 (0.996–1.175)	0.063
Steroid for 2 weeks	0.032 (0.005–0.224)	0.001
Hydrocephalus	4.977 (1.345–18.410)	0.016

[a]Duration between the onset of presenting clinical features and the start of antituberculous therapy. CI=Confidence interval; CNS=central nervous system; CSF=cerebrospinal fluid; TB-PCR=tuberculosis polymerase chain reaction; WBC=the white blood cell count; TBM=tuberculous meningitis.

Discussion

Tuberculosis is an endemic disease in Taiwan, and TBM is an important public health issue. The overall 9-month mortality rate in this study was 38.9% (42/108), which is similar to the mortality rate reported by Roca and Tornador.[3] The three most common symptoms of our TBM patients on admission were fever, consciousness disturbance, and headache. Consciousness disturbance was statistically correlated to mortality. We also found that old age, which has been shown to correlate with poor outcomes in previous studies[16,17] was also a factor in our study. The deaths in this study tended to be among the elderly (65.5 *vs.* 48.2 years, $p<0.001$), supporting the relationship between age and mortality in patients with TBM. The staging of TBM depends on the neurological signs and state of consciousness on admission. Previous studies indicate a correlation between the severity of TBM and poor outcome,[2,4,17] and this is confirmed by our study ($p=0.006$). Stage III disease resulted in a higher mortality rate than stage I, but there was no significant difference

Table 4. Management in patients with hydrocephalus

	Deceased ($n=30$)	Survived ($n=18$)	Univariate p
Steroid	9 (30.0)	15 (83.3)	<0.001
Mannitol	12 (40.0)	9 (50.0)	0.499
Shunting or drainage	7 (23.3)	6 (33.3)	0.450

between stages I and II. The timing of the start of anti-TB therapy was also an important factor that influenced the outcome.[8,9] In this study, we found that deceased patients in the "definite" group had experienced greater delay in receiving treatment compared with those that survived. Early anti-TB therapy reduced the mortality rate in all patients as assessed by univariate analysis. Hence, early diagnosis and treatment are essential to avoid serious co-morbidity.

Previous studies show that the prognostic factors for TBM include CSF glucose levels, protein and lactate levels, and the presence of extra-CNS tuberculosis,[6,17] but this was not confirmed by our study ($p=0.764$, $p=0.312$, $p=0.110$ and $p=0.074$, respectively; Table 2). Age, comatose mental status, cranial nerve palsy, stage of TBM, delayed or interrupted treatment, and hydrocephalus have all been reported to be predictors for mortality by logistic regression analysis.[6,7] In this study, old age and hydrocephalus (identified by the imaging studies) carried an increased risk of death. Multivariate logistic regression analysis identified adjunctive steroid therapy as a protective factor, (Table 4).

The increase in the incidence of drug-resistant *M. tuberculosis* strains causes a serious problem worldwide, and makes therapy difficult, especially in developing countries. This study shows that 14.6% (6/41) of culture-proved TBM cases were resistant, which is similar to previous reports from Taiwan.[6,18] Only one patient infected with a multiple drug-resistant strain died. There was no significant correlation between the resistant strains and mortality ($p=0.182$), but the result still raises our attention to this problem.

Positive *M. tuberculosis* culture from CSF was associated with a poor prognosis,[5] and this observation may indicate that higher microbe loading and burden led to an increased risk of developing consciousness disturbances, hydrocephalus, more serious TBM stages, and subsequent mortality in the "definite" group compared with the "probable" group. Univariate analysis showed that, in the "definite" group, consciousness disturbance and old age were correlated with an increased mortality rate. However, comparison of the TBM stage did not show any statistical differences in mortality (Table 2). However, the small number of patients in the "definite" group may make it difficult to clarify the relationship between TBM stage and mortality.

Brain CT or MRI studies of TBM patients may show hydrocephalus, parenchymal enhancement, contrast enhancement of basal cisterns, cerebral infarct, focal or diffuse brain edema, abscess or tuberculoma;[19] and hydrocephalus is known to be an important predictor for outcome.[7] In this study, hydrocephalus was the most common finding in the imaging studies and was associated with poor outcome. Hence, the management of hydrocephalus is an important issue for TBM patients. However, the indications for the implantation of V-P shunts, or CSF drainage, for TBM remain controversial. The usefulness of V-P shunts is debatable, although some authors suggest that a rapid deterioration of consciousness might be caused by ventricular dilation, and that early shunting remains the best option to prevent long-term neurological sequelae and improve the clinical outcome.[20,21] Conversely, some studies show that drainage does not alter the course of disease, and might even result in the added complication of CNS diversion.[22] In this study, 48 patients had hydrocephalus, which improved after steroid therapy. However, V-P shunts, CSF drainage, and mannitol use were not associated with improved mortality. Steroid treatment is thought to decrease the severity of hydrocephalus, but as most patients in our study did not receive subsequent CT/MRI follow-ups, we cannot evaluate the relationship between steroid treatment and hydrocephalus.

This study shows that mortality was reduced in both the "definite" and "probable" groups if they received prednisolone ≥ 20 mg/day over a 2-week period. Some studies report that steroids modulate acute CSF protein concentration, and reduce interferon-gamma concentrations, cell counts and cerebral edema.[23,24] We retrospectively traced the records of patients who had two or more CSF work-ups ($n=66$), and found that most patients treated

with steroids had decreased CSF protein concentrations compared with those who did not receive steroids (83.3% *vs.* 57.1%; $p=0.030$). However, the white cell count, and the glucose and lactate levels in CSF showed no statistical correlation with steroid treatment, and it is not clear for how long steroids should be used. Some studies suggest giving steroids for at least 7–10 days,[11] but some suggest as long as 8 weeks.[12] Our data show that the mortality rate was reduced when using steroids over 2–4 weeks, and was associated with clinical improvement. However, there was no significant difference in survival when steroids were used for 4 weeks. Perhaps giving steroids for 2–4 weeks is the optimal for TBM, but there is still room for further work in this area, especially as the dosage and duration of steroid therapy varied in our study.

In conclusion, old age, consciousness changes, TBM stage III, and hydrocephalus suggest a poor prognosis for TBM, as does isolation of *M. tuberculosis* from the CSF, or positive CSF TB-PCR. In addition, delay in giving anti-TB therapy has a significant influence on mortality, and early diagnosis and prompt treatment play a key role in survival. Steroid therapy improves the survival rate in adult TBM, especially in those patients with hydrocephalus. Therefore, adjunctive steroid therapy should be administered for at least 2 weeks. However, the optimal dose and duration of steroid therapy need to be investigated further.

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