Int J Clin Exp Med 2015;8(3):4487-4493
www.ijcem.com /ISSN:1940-5901/IJCEM0005059

Original Article

Prognostic factors of tuberculous meningitis: a single-center study

Jin Gu, Heping Xiao, Furong Wu, Yanping Ge, Jun Ma, Wenwen Sun

Clinic and Research Center of Tuberculosis, Shanghai Key Lab of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, China

Received December 19, 2014; Accepted February 25, 2015; Epub March 15, 2015; Published March 30, 2015

Abstract: Objective: To investigate the prognostic factors of tuberculous meningitis (TBM) and develop strategies for the improvement of clinical efficacy. Methods: A total of 156 TBM patients were retrospectively reviewed. The demographic characteristics, underlying diseases, clinical features, laboratory findings, bacteriologic test, images, use of steroids, mannitol and anti-TB drugs, surgery or drainage, and clinical outcomes were collected and analyzed. Results: Patients with tubercle bacillus in the cerebrospinal fluid had significantly higher rate of consciousness disturbance (78.8%) and greater proportion of Glasgow coma scale (GCS) score of 3 (37.9%) when compared with the possible TBM patients (51.1% and 13.3%, respectively). Patients with definite TBM had a poor outcome and their mortality was significantly higher than in possible TBM patients (42.4% vs. 17.8%, $P < 0.05$). Univariate regression analysis showed that the advanced age, concomitant hematogenous disseminated pulmonary tuberculosis, change in consciousness, low GCS score on admission and hydrocephalus were associated with a poor prognosis; timely anti-TB treatment and reasonable hormone applications predicted a favorable outcome. Multivariate regression analysis showed that advanced age, change in consciousness, low GSC score and concomitant hydrocephalus were independent risk factors of TBM, and use of prednisone at ≥ 60 mg/d was protective factor for TBM (P=0.003, OR=0.013). Conclusions: The advanced age, changes in consciousness, low GCS score on admission and concomitant hydrocephalus are independent risk factors of TBM. For patients with risk factors, diagnostic anti-TB therapy and reasonable hormone therapy should be performed timely to reduce mortality and disability.

Keywords: Tuberculous meningitis, prognosis, prognostic factors

Introduction

Tuberculous meningitis (TBM) is a non-suppurative inflammatory disease of the dura mater and spinal cord meninge caused by tubercle bacillus. About 5-15% of extrapulmonary tuberculosis involves the nervous system. TBM is a major one of extrapulmonary tuberculosis with involvement of the nervous system and accounts for about 70% of nervous system tuberculosis. TBM has an insidious onset and atypical clinical manifestations. Thus, it is usually in its advanced stage when it is diagnosed, which results in a poor therapeutic efficacy and often causes severe extrapulmonary tuberculosis with high mortality [1-4]. In recent years, with the increased drug resistance of tubercle bacillus [5], delayed development of anti-TB drugs and increased HIV patients [6, 7], the morbidity and mortality of TB are also increasing over year. To investigate the prognostic factors of TBM and to increase the clinical therapeutic efficacy, TBM patients from our hospital were retrospectively reviewed.

Patients and methods

Data collection

From January 2008 to September 2012, a total of 156 patients diagnosed with TBM were treated in our hospital and retrospectively reviewed in this study. Following information was collected: demographic characteristics, baseline diseases, clinical characteristics, laboratory findings, bacteriological results, imaging manifestation, use of steroids, mannitol and anti-TB drugs, surgery or drainage, and clinical outcomes. Most patients had spinal cord fluids (CSF) taken on admission, and the following

Table 1. Demographics and clinical characteristics of TBM patients

Characteristics	Definite TBM (n=66)	Suspicious TBM (n=90)	All patients (n=156)	t	*P*
Age	36.7±19.2	33.7±18.2	32.9±18.6	0.994	0.322
Gender (M)	39 (59.1)	59 (65.7)	98 (62.8)	0.681	0.409
Clinical manifestations					
Fever	53 (80.3)	74 (82.2)	127 (81.4)	0.093	0.761
Consciousness disturbance	52 (78.8)	46 (51.1)	98 (62.8)	12.488	0.000
Headache	36 (54.5)	58 (64.4)	94 (60.3)	1.558	0.212
Vomiting	46 (69.7)	61 (67.8)	106 (68.6)	0.065	0.799
Stiff neck	30 (45.5)	55 (61.1)	85 (54.5)	3.764	0.052
Hematogenous disseminated tuberculosis	27 (40.9)	20 (22.2)	47 (30.1)	6.316	0.012
Grade on admission					
I	7 (10.6)	32 (35.6)	39 (25.0)	19.154	0.000
I	34 (51.5)	46 (51.1)	80 (51.3)		
III	25 (37.9)	12 (13.3)	37 (23.7)		
CSF					
Pressure > 20 mmH_2O	59 (89.4)	78 (84.8)	137 (86.7)	0.709	0.400
WBC ($\times 10^6$/L)	22±31	22±32	22±31	0.0452	0.964
Protein (mg/L)	3463±5481	2937±3342	3162±4346	0.7420	0.459
Glucose (mmol/L)	2.4±1.9	2.6±1.6	2.5±1.7	0.8284	0.409
Chloride (mmol/L)	115.35±5.3	116.3±10.1	115.9±7.4	-0.6966	0.487
ADA (IU/L)	9.37±4.7	7.91±5.9	8.53±4.0	1.660	0.099
Imaging examination					
Hydrocephalus	42 (63.6)	42 (46.7)	84 (53.8)	4.412	0.036
Cerebral infarction	15 (22.7)	22 (24.4)	37 (23.7)	0.062	0.803
Manifestations of TBM[a]	18 (27.3)	30 (33.3)	48 (30.8)	0.657	0.418
Outcome					
Poor	35 (53.0)	25 (27.8)	60 (38.5)	10.259	0.001
Death	28 (42.4)	16 (17.8)	44 (28.2)	11.422	0.001
Interval between admission and death (d)	75.3±69.1	68.2±49.8	71.2±57.4	0.7460	0.457

Footnotes: a: multiple manifestations of TBM: exudation of basal cistern, hydrocephalus, meningeal enhancement, tuberculoma, vasculitis, abscess or infarction; TBM = tuberculous meningitis; CSF = spinal cord fluids; WBC = white blood cell; ADA = adenosine deaminase.

tests performed: total cell count, cytological classification, detection of glucose, proteins, chlorides, and adenosine deaminase (ADA) as well as TB-PCR and TB smearing and culture. In addition, chest radiography and brain computed tomography or magnetic resonance imaging (MRI) examinations were performed.

Diagnostic criteria

TBM was diagnosed according to the clinical characteristics, and findings from routine and biochemical CSF examination, TB smearing and culture and cerebral imaging examinations [8]. Patients were diagnosed with definite TBM and suspicious TBM, and the mortality and clinical severity of TBM were compared between two groups. For patients with definite TBM, TB was found in CSF by CSF smearing and culture or TB-PCR [9]. For patients with suspicious TBM, the characteristics of tuberculous CSF should be found (white blood cells > 10×10^6/L [mainly lymphocytes]; protein > 40 mg/dl; reduced ratio of CSF glucose to serum glucose [< 0.6 or < 60 mg/dl]), and at least one of following findings was present: (1) hematogenous disseminated pulmonary tuberculosis: tubercle bacillus was separated from other tissues except for CSF, or active pulmonary tuberculosis was present; (2) Imaging findings: cerebral CT or MRI showed characteristics of TBM; (3) history of past illness: TB infection or exposure to TB;

Table 2. Prognostic factors of TBM patients in two groups

Variables	Definite TBM (n=66)			Suspicious TBM (n=90)			All patients (n=156)		
	Poor (n=35)	Good (*n*=31)	P	Poor (n=25)	Good (*n*=65)	P	Poor (n=60)	Good (*n*=96)	*P*
Age (yr)	38.3±7.6	30.1±6.6	0.029	40.9±6.6	29.9±7.6	0.000	40.1±5.3	29.1±5.2	0.000
Age > 60 yr	22 (62.9%)	10 (32.3%)	0.013	18 (72.0%)	20 (30.0%)	0.000	38 (63.3%)	28 (29.2%)	0.000
Male	23 (65.7%)	16 (51.6%)	0.245	15 (60.0%)	44 (67.7%)	0.492	38 (63.3%)	60 (62.5%)	0.917
CNS tuberculosis	17 (48.6%)	10 (32.3%)	0.179	7 (28.0%)	13 (20.0%)	0.414	24 (40.0%)	23 (24.0%)	0.034
Clinical manifestations									
Fever	29 (82.9%)	24 (77.4%)	0.579	24 (96.0%)	50 (76.9%)	0.034	53 (88.3%)	74 (77.1%)	0.079
Headache	16 (45.7%)	20 (64.5%)	0.126	16 (64.0%)	42 (64.6%)	0.956	32 (53.3%)	62 (64.6%)	0.162
Consciousness disturbance	30 (85.7%)	22 (71.0%)	0.144	17 (68.0%)	29 (44.6%)	0.047	47 (78.3%)	51 (53.1%)	0.002
Stiff neck	14 (40.0%)	16 (51.6%)	0.344	14 (56.0%)	41 (63.1%)	0.537	28 (46.7%)	57 (59.4%)	0.121
CSF examination									
Pressure > 20 mmH_2O	29 (82.9%)	30 (96.9%)	0.067	24 (96.0%)	54 (83.1%)	0.106	53 (88.3)	84 (87.5%)	0.877
WBC ($\times 10^6$/L)	23±36	22±24	0.908	22±22	22±23	0.921	23±32	21±34	0.652
Protein (mg/L)	3510±5674	3419±3543	0.936	3012±3462	2874±4652	0.8933	3331±4613	3056±4541	0.879
Glucose (mmol/L)	2.0±2.0	2.8±2.1	0.065	2.4±1.3	2.7±1.9	0.5183	2.2±1.7	2.7±1.8	0.467
Chloride (mmol/L)	114.8±3.4	116.0±9.8	0.407	115.1±8.5	116.8±3.1	0.1656	114.4±7.6	116.8±9.4	0.098
ADA (IU/L)	11.2±6.3	8.5±5.5	0.070	9.7±5.1	7.5±4.8	0.059	10.3±5.3	8.9±4.0	0.063
GCS grade									
I	3 (8.6%)	4 (12.9%)	0.163	8 (32.0%)	24 (36.9%)	0.855	11 (18.3%)	28 (29.2%)	0.025
II	15 (42.9%)	19 (61.6%)		13 (52.0%)	33 (50.8%)		28 (46.7%)	52 (54.2%)	
III	17 (48.6%)	8 (25.8%)		4 (16.0%)	8 (12.3%)		21 (35.0%)	16 (16.7%)	
Duration of anti-TB therapy (d)[a]	15.9	12.6	0.176	20.6	12.5	0.127	18.2	12.6	0.044
Use of steroid (Prednisone)									
≥ 30 (mg/d)	12 (34.3%)	19 (61.3%)	0.028	8 (32.0%)	29 (44.6%)	0.276	20 (33.3%)	48 (50.0%)	0.041
≥ 60 (mg/d)	2 (5.7%)	14 (45.2%)	0.000	3 (12.0%)	25 (38.5%)	0.021	5 (7.6%)	39 (43.3%)	0.000
≥ 90 (mg/d)	2 (5.7%)	13 (41.9%)	0.004	2 (8.0%)	13 (20.0%)	0.219	4 (6.1%)	26 (28.9%)	0.000
≥ 120 (mg/d)	2 (5.7%)	5 (16.1%)	0.170	1 (4.0%)	6 (9.2%)	0.668	3 (4.5%)	11 (12.2%)	0.097
Dehydration treatment with mannitol	11 (31.4%)	11 (35.5%)	0.727	7 (28.0%)	20 (30.8%)	0.797	18 (30.0%)	31 (32.3%)	0.764
Imaging findings	(n=32)	(n=27)		(n=26)	(n=52)		(n=58)	(n=79)	
Hydrocephalus	25 (78.1%)	13 (48.1%)	0.017	19 (73.1%)	13 (25.0%)	0.000	44 (75.9%)	26 (32.9%)	0.000
Cerebral Infarction	10 (31.2%)	3 (11.1%)	0.063	6 (23.1%)	13 (25.0%)	0.852	16 (27.6%)	16 (20.3%)	0.316
Manifestations of TBM	6 (18.8%)	10 (37.0%)	0.115	10 (38.5%)	16 (30.8%)	0.497	16 (27.6%)	26 (32.9%)	0.504

Footnotes: a: interval between presence of symptoms and anti-TB therapy in TBM patients; TBM = tuberculous meningitis; CNS = central nerve system; CSF = spinal cord fluids; WBC = white blood cell; ADA = adenosine deaminase; GCS = Glasgow coma scale; TB = tuberculosis.

(4) Diagnostic therapy: symptoms improved significantly after anti-TB therapy. The severity of TBM was determined according to the TBM grading system developed by the British Medical Research Council: grade I equivalent to Glasgow Coma Scale (GCS) 15, indicating no focal nervous system signs; grade II equivalent to GCS 15, accompanied by nervous dysfunction, or GSC 11-14; grade III equivalent to GCS ≤ 10 [10].

Therapeutic protocol

Patients were treated with at least 4-7 anti-TB drugs: isoniazid (INH): 300-1200 mg/d; rifampicin (RFP): 450-600 mg/d; pyrazinamide (PZA): 1500 mg/d; ethambutol: (EMB): 750 mg/d. Therapy was done for at least 12 months unless patients died or side effects were present. Other anti-TB drugs included levofloxacin (LFX, 500-600 mg/d), moxifloxacin (400 mg/d), amikacin (400-600 mg/d) and protionamide (Pto; 600 mg/d). These drugs were used in the intensive phase of anti-TB therapy or when side effects were observed. The dose of steroids was equivalent to ≥ 30 mg/d prednisone, and steroids therapy continued for at least 2 weeks, followed by the decrement of steroid dose. Dehydration treatment with mannitol or surgical intervention was performed when the elevated intracranial pressure or hydrocephalus was present.

Therapeutic outcome

Therapeutic outcome was categorized into 4 types: 1) normal: the motor function, intelli-

Table 3. Multivariate regression analysis of prognostic factors in TBM patients

Risk factor	Odds ratio (95% CI)	*P*
Age	1.032 (1.013-1.081)	0.038
Hematogenous disseminated tuberculosis	0.998 (0.321-4.789)	0.779
Consciousness disturbance	1.063 (1.016-9.902)	0.029
GCS grade on admission	1.674 (1.347-5.031)	0.038
Time of anti-TB therapy	1.021 (0.956-1.316)	0.068
Prednisone ≥ 60 (mg/d)	0.013 (0.001-0.211)	0.003
Hydrocephalus	5.031 (1.389-13.347)	0.023

Footnotes: GCS = Glasgow coma scale; TB = tuberculosis.

Table 4. Clinical outcome of patients with hydrocephalus

	Poor outcome (n=44)	Good outcome (n=26)	*P*
Prednisone ≥ 60 (mg/d)	12 (27.3%)	22 (84.6%)	0.000
Dehydration treatment	17 (38.6%)	13 (50.0%)	0.353
Surgery	10 (22.7%)	9 (34.6%)	0.280

gence, vision and hearing were normal; 2) mild sequelae: hemiplegia, mild intelligence reduction, vision and/or hearing dysfunction; 3) severe sequelae: quadriplegia, severe intellectual impairment, blindness and/or deafness; 4) death. Types 1 and 2 were regarded as good outcomes, and types 3 and 4 as poor outcomes.

Statistical analysis

Logistic regression analysis was employed to evaluate the survival of these patients (mortality within 12 months). To exclude confounding factors affecting survival, variables with P ≤ 0.05 in univariate analysis were included into multivariate analysis with logistic regression model for further analysis. Statistical analysis was performed with SPSS version 17.0. Results were expressed as adjusted OR and corresponding 95% confidence interval (CI). A value of P < 0.05 was considered statistically significant.

Results

Clinical manifestation and laboratory characteristics

Among these patients with tubercle bacillus in the CSF, the incidence of consciousness disturbance was 78.8%, and patients with GCS grade III accounted for 37.9%, which were significantly higher than those in suspicious TBM patients (51.1% and 13.3%, respectively; P < 0.05); the mortality was as high as 42.4%, suggesting a poor prognosis, which was significantly higher than that in suspicious TBM patients (17.8%; P < 0.05). Moreover, patients with definite TBM usually had markedly higher incidences of concomitant hematogenous disseminated tuberculosis and hydrocephalus (P < 0.05). The demographics and biochemical findings of CSF were comparable between two groups (**Table 1**).

Factors influencing prognosis

As shown in **Table 2**, factors related to a poor prognosis included: advanced age, concomitant hematogenous disseminated tuberculosis, consciousness disturbance, low GCS score on admission and hydrocephalus. Old patients had relatively poor outcome. Of patients older than 60 years, as high as 63.3% had a poor prognosis (*P*=0.000), suggesting age is one of factors predicting a poor prognosis. Consciousness disturbance is a common clinical manifestation of TBM and had an incidence of 78.3% in TBM patients with a poor prognosis (*P*=0.002). Among patients with severe TBM on admission, a low GCS score significantly influenced the prognosis of TBM and was a factor predicting a poor prognosis (*P*=0.025). Concomitant tuberculosis at other sites (especially the hematogenous disseminated tuberculosis or widespread systemic tuberculosis [bone tuberculosis, abdominal tuberculosis, lymph node tuberculosis]) predicted a poor prognosis (*P*=0.034). In addition, hydrocephalus was found in 75.9% of patients with a poor prognosis, which was significantly higher than that in patients with a good prognosis (*P*=0.000).

Factors predicting a good prognosis included: timely anti-TB therapy and rational use of steroids. As shown in **Table 2**, the median time interval between presence of symptoms and anti-TB therapy was 12.6 days in TBM patients with a good prognosis, which was shorter than that in TBM patients with a poor prognosis (18.2 days). Use of prednisone at 30-90 mg/d

could improve the prognosis of TBM, but prednisone at ≥ 120 mg/d had less influence on the therapeutic efficacy.

Factors with P ≤ 0.05 in univariate analysis were included into multivariate analysis with logistic regression model, and results showed advanced age, consciousness disturbance, low GCS score on admission and hydrocephalus were independent risk factors of TBM prognosis. However, use of prednisone at ≥ 60 mg/d was a protective factor for TBM prognosis (*P*=0.003, OR=0.013) (**Table 3**).

Treatment and prognosis of hydrocephalus

Hydrocephalus is a common complication of TBM and also a factor predicting a poor prognosis. Thus, the association between management of hydrocephalus and TBM prognosis was evaluated. Results showed 84.6% of hydrocephalus patients with a good prognosis used prednisone ≥ 60 mg/d, which was significantly higher than that in patients with a poor prognosis (27.3%; *P*=0.000). This suggests that high dose steroid may markedly improve the prognosis of hydrocephalus. For hydrocephalus patients, the use of dehydration treatment with mannitol and surgery had less influence on the prognosis of TBM (**Table 4**).

Discussion

Our results showed TBM had a higher incidence in the middle-young age (mean age: 32.9±18.6 years) and in males (62.8%). The most common clinical manifestations of TBM were fever (81.4%), consciousness disturbance (62.8%) and vomiting (68.6%), but the incidences of headache and stiff neck were slightly higher than 50% (60.3% and 54.5%, respectively). These findings suggest that the onset of TBM is insidious and it has non-specific manifestations, resulting in difficulty in its diagnosis. Patients with definite TBM usually presented evident consciousness disturbance (78.8%) and had more severe TBM (GCS grade III: 37.9%) and a poor prognosis (mortality of 42.4% within 12 months). Wang et al [11] reported that the presence of tubercle bacillus in CSF was related to a poor prognosis, which may be explained that the increased microbial load may elevate the risk for consciousness disturbance. In addition, the risk for a poor prognosis also increases over age in TBM patients. Of TBM patients older than 60 years, 63.3% had a poor prognosis, and advanced age was found to be an independent risk factor of a poor prognosis.

About 1/3 of TBM patients had atypical manifestations, and a majority of TBM patients had increased CSF pressure (CSF pressure > 20 mmH_2O in 86.7%). Increases in total cell count, protein and ADA and reductions in glucose and chlorides were also observed in TBM patients, but these changes were comparable between definite TBM patients and suspicious patients and had less influence on the prognosis of TBM.

The cranial imaging findings of TBM patients are usually diverse and non-specific. These findings include the exudation of basal cistern, hydrocephalus, meninges enhancement, tuberculoma, vasculitis, abscess or cerebral infarction, showing the involvement of meningeal surface, CSF space, blood vessels and nerves. In early phase of TBM, cranial CT may display the extent of lesions (mainly the exudative lesions) and pia mater enhancement. In late phase, cranial CT may show the features of obstructive hydrocephalus. Cranial MRI is more sensitive than CT, especially for lesions involving the brainstem or meninge [12, 13]. Santy et al [14] showed the lipid peak of TBM lesions was higher in the images of MRI, which was helpful to differentiate tuberculous lesions from non-tuberculous lesions in the brain. In our study, about 53.8% of TBM patients had concomitant hydrocephalus to different extents, which is usually a consequence of the obstruction of CSF and increased intracranial pressure [15]. This also suggests, in middle to late phase of TBM, hydrocephalus is an independent risk factor of a poor prognosis, which was consistent with previously reported by Misra et al [16]. In addition, more than 30.1% of TBM patients had concomitant hematogenous disseminated tuberculosis, and thus routine chest X ray or CT is recommended for patients with suspicious TBM. For patients with concomitant hematogenous disseminated tuberculosis, severe TB, widespread systemic tuberculosis, nausea, vomiting, headache or fever non-responsive to therapy, cranial CT or MRI and CSF examination are recommended for the early diagnosis of TBM.

Our results showed the time interval between presence of symptoms and anti-TB therapy was

12.6 days in TBM patients with a good prognosis, which was 1 week earlier when compared with TBM patients with a poor prognosis (18.2 days). This suggests that early therapy is crucial to increase the therapeutic outcome, and reduce mortality and disability (P=0.044). Steroids have been accepted as a drug in the anti-TB therapy [17, 18], but the dose of steroids is still empirically determined. Our results showed the use of prednisone at 30-90 mg/d could improve the prognosis of TBM (P=0.041~0.000). However, prednisone at ≥ 120 mg/d had less influence on the therapeutic outcome, or even increased the probability of side effects. Thus, high dose steroids are not recommended in TBM patients. Therapy of hydrocephalus is a challenge for clinicians. Raut et al [19] reported that hydrocephalus occurred in approximately two-third of patients with tuberculous meningitis and had an unfavorable impact on the prognosis. In the regular anti-TB therapy, dehydration is routinely used. For patients with refractory increased intracranial pressure or severe ventriculomegaly, surgery is performed if necessary. Our results showed that steroids at a high dose might improve the prognosis of hydrocephalus (P=0.000). There is still controversy on the use of surgery for hydrocephalus, and the available results are conflicting among studies, which may be ascribed to the timing and methods of surgery as well as complications [20-22]. In our study, surgery had less influence on the prognosis of TBM. In addition, dehydration therapy with mannitol was also not related to the prognosis of TBM.

Taken together, factors predicting a poor prognosis of TBM are advanced age, concomitant tuberculosis at other sites, consciousness disturbance, low GCS score on admission, and hydrocephalus; factors predicting a good prognosis of TBM include timely anti-TB therapy and rational use of steroids. Of these factors, advanced age, consciousness disturbance, low GCS score on admission, and hydrocephalus are independent risk factors of TBM prognosis, but prednisone at ≥ 60 mg/d is a protective factor for TBM. Clinicians should pay attention to the monitoring of clinical manifestations of TBM. For suspicious TBM patients with above risk factors, timely diagnostic anti-TB therapy and steroids therapy are recommended.

Disclosure of conflict of interest

None.

Address correspondence to: Heping Xiao, Clinic and Research Center of Tuberculosis, Shanghai Key Lab of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, China. E-mail: xiaoheping_feike@163.com

References

[1] Sütlaş PN, Ünal A, Forta H, Şenol S and Kırbaş D. Tuberculous meningitis in adults: review of 61 cases. Infection 2003; 31: 387-391.

[2] Roca B, Tornador N and Tornador E. Presentation and outcome of tuberculous meningitis in adults in the province of Castellon, Spain: a retrospective study. Epidemiol Infect 2008; 136: 1455-1462.

[3] Qureshi HU, Merwat SN, Nawaz SA, Rana AA, Malik A, Mahmud MK, Latif A, Khan A and Sarwari AR. Predictors of inpatient mortality in 190 adult patients with tuberculous meningitis. J Pak Med Assoc 2002; 52: 159-163.

[4] Gunawardhana S, Somaratne SC, Fernando MAH and Gunaratne PS. Tuberculous meningitis in adults: a prospective study at a tertiary referral centre in Sri Lanka. Ceylon Med J 2013; 58: 21-25.

[5] Vinnard C, Winston CA, Wileyto EP, MacGregor RR and Bisson GP. Isoniazid resistance and death in patients with tuberculous meningitis: retrospective cohort study. BMJ 2010; 341: c4451.

[6] Alvarez-Uria G, Naik PK, Pakam R, Bachu L and Midde M. Natural History and Factors Associated with Early and Delayed Mortality in HIV-Infected Patients Treated of Tuberculosis under Directly Observed Treatment Short-Course Strategy: A Prospective Cohort Study in India. Interdiscip Perspect Infect Dis 2012; 2012: 502012.

[7] Efsen AMW, Panteleev AM, Grint D, Podlekareva DN, Vassilenko A, Rakhmanova A, Zeltina I, Losso MH, Miller RF and Girardi E. TB Meningitis in HIV-Positive Patients in Europe and Argentina: Clinical Outcome and Factors Associated with Mortality. Biomed Res Int 2013; 2013: 373601.

[8] Ahuja GK, Mohan KK, Prasad K and Behari M. Diagnostic criteria for tuberculous meningitis and their validation. Tuber Lung Dis 1994; 75: 149-152.

[9] Panagariya A, Sureka RK, Ralot T, Sharma B and Dubey P. Clinicodiagnostic features of tuberculous meningitis and the role of CSF PCR in early diagnosis: a study from north-west India. J Indian Med Assoc 2013; 111: 309-312, 314.

[10] Byrd T and Zinser P. Tuberculosis meningitis. Curr Treat Option Neurol 2001; 3: 427-432.

[11] Wang JT, Hung CC, Sheng WH, Wang JY, Chang SC and Luh KT. Prognosis of tuberculous men-

ingitis in adults in the era of modern antituberculous chemotherapy. J Microbiol Immunol Infect 2002; 35: 215-222.
[12] van der Merwe DJ, Andronikou S, Van Toorn R and Pienaar M. Brainstem ischemic lesions on MRI in children with tuberculous meningitis: with diffusion weighted confirmation. Childs Nerv Syst 2009; 25: 949-954.
[13] Yuan H, Wang AL, Lin SQ, Qiu XW, Zhu WP and Wu LH. MRI in diagnosis of tuberculous meningitis. Chin J Nosocomiol 2013; 23: 3085-3087.
[14] Santy K, Nan P, Chantana Y, Laurent D, Nadal D and Richner B. The diagnosis of brain tuberculoma by 1H-magnetic resonance spectroscopy. Eur J Pediatr 2011; 170: 379-387.
[15] Schoeman JF, Laubscher JA and Donald PR. Serial lumbar CSF pressure measurements and cranial computed tomographic findings in childhood tuberculous meningitis. Childs Nerv Syst 2000; 16: 203-208.
[16] Misra UK, Kalita J, Srivastava M and Mandal SK. Prognosis of tuberculous meningitis: a multivariate analysis. J Neurol Sci 1996; 137: 57-61.
[17] Simmons CP, Thwaites GE, Quyen NTH, Chau TTH, Mai PP, Dung NT, Stepniewska K, White NJ, Hien TT and Farrar J. The clinical benefit of adjunctive dexamethasone in tuberculous meningitis is not associated with measurable attenuation of peripheral or local immune responses. J Immunol 2005; 175: 579-590.
[18] Török ME, Bang ND, Chau TTH, Yen NTB, Thwaites GE, Quy HT, Dung NH, Hien TT, Chinh NT and Hoang HTT. Dexamethasone and long-term outcome of tuberculous meningitis in Vietnamese adults and adolescents. PLoS One 2011; 6: e27821.
[19] Raut T, Garg RK, Jain A, Verma R, Singh MK, Malhotra HS, Kohli N and Parihar A. Hydrocephalus in tuberculous meningitis: Incidence, its predictive factors and impact on the prognosis. J Infect 2013; 66: 330-337.
[20] Chen C, Peng J, He F, Liu JP and Yin F. Clinical analysis of ventriculoperitoneal shunt for grade IV tuberculous meningitis children with hydrocephalus. J Appl Clin Ped 2013; 28: 471-473.
[21] Sil K and Chatterjee S. Shunting in tuberculous meningitis: a neurosurgeon's nightmare. Childs Nerv Syst 2008; 24: 1029-1032.
[22] Lamprecht D, Schoeman J, Donald P, Hartzenberg H. Ventriculoperitoneal shunting in childhood tuberculous meningitis. Br J Neurosurg 2001; 15: 119-125.