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Prognosis of tuberculous meningitis in adults in the era of modern antituberculous chemotherapy

Jann-Tay Wang[1], Chien-Ching Hung[1], Wang-Huei Sheng[1], Jann-Yuan Wang[1], Shan-Chwen Chang[1], Kwen-Tay Luh[2]

Departments of [1]Internal Medicine and [2]Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan, ROC

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This study reviewed the clinical manifestations and outcome of tuberculous meningitis in the era of modern antituberculous chemotherapy and applied these data in assessing the role of clinical staging evaluated 30 days after treatment in predicting long-term outcome. A total of 41 adult patients with tuberculous meningitis hospitalized at a university hospital in Taiwan from June 1994 through August 1999 were included in this retrospective study. Their age ranged from 16 to 80 years (median, 41 years), and 17 (41.5%) patients had had a variety of underlying immunocompromising diseases. Fever (90%), headache (75.6%), neck stiffness (68.3%), altered consciousness (26.8%), and nausea and/or vomiting (26.8%) were the leading initial presentations. During the treatment course, 19 patients experienced new neurologic complications. The overall case fatality rate was 9.8% and morbidity rate 56.1%. More advanced clinical stage evaluated at 30 days after initiation of antituberculous chemotherapy and positive cerebrospinal fluid culture for *Mycobacterium tuberculosis* were the only 2 factors significantly associated with a worse long-term prognosis. Results indicate that tuberculous meningitis is associated with a high morbidity, consisting of minor and major neurologic sequelae, despite modern antituberculous chemotherapy. In addition, more advanced clinical staging evaluated at 30 days after the start of antituberculous chemotherapy and a positive cerebrospinal fluid culture for *M. tuberculosis* were associated with a poor prognosis.

Key words: Tuberculous meningitis, prognosis, antituberculous chemotherapy

Tuberculosis (TB) remains one of the most common infectious diseases associated with significant morbidity and fatality worldwide. The World Health Organization estimated that one-third of the world's population had been infected with *Mycobacterium tuberculosis* [1]. In 1990, it was estimated that there were 7.5 million cases of TB with 2.5 million deaths worldwide [2]. In Taiwan, the prevalence of radiographically suspected TB was 0.65% in adults over 20 years in age in 1993, and the incidence of TB was 71.12 per 100 000 in 1997 [3].

Tuberculous meningitis, one of the most devastating forms of TB, accounts for 7% to 12 % of all types of TB [4]. Despite the introduction of anti-TB chemotherapy, fatality and morbidity rates of TB meningitis remain high, ranging from 7% to 63% and 8.3% to 17.6%, respectively [5-14]. The wide ranges of morbidity and fatality rates reported in studies published in the 1990s might have been related to diverse study populations consisting of both children and adult patients, different timing of initiation of anti-TB therapy, and different treatment regimens among the studies or even within the same study.

The British Medical Research Council (BMRC) has established a staging schema to classify neurologic complications of TB meningitis [15]. According to this staging schema, some previous studies demonstrated that more advanced clinical stage at presentation and/or initiation of treatment was associated with a worse prognosis [5,8,9,11,14], while other reports had contrary findings [12,13]. In addition, development of new neurologic complications during effective treatment for TB meningitis has been also reported [16-18]. Whether reevaluation of the neurologic staging some time after initiation of anti-TB chemotherapy would be better correlated with outcome has not been investigated. Therefore, this study evaluated the clinical manifestations and outcome of TB meningitis after treatment with modern anti-TB chemotherapy including isoniazid, rifampin, pyrazinamide, and ethambutol, and assessed the role of reevaluation of clinical staging 30 days after initiation of anti-TB chemotherapy in predicting long-term outcome.

Corresponding author: Dr. Shan-Chwen Chang, Section of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, No. 7 Chung-Shan South Road, Taipei, 100, Taiwan, ROC. E-mail: sc4030@ha.mc.ntu.edu.tw

Patients and Methods

From June 1994 through August 1999, hospitalized patients aged over 15 years with a diagnosis of TB meningitis at National Taiwan University Hospital (NTUH), an 1800-bed medical center providing both primary and tertiary care in Taiwan, were included in this study.

Data collection

A standardized case record form was used to collect clinical and laboratory data, as well as the result of radiologic study of the central nervous system (CNS). Neurologic status was evaluated at presentation, start of anti-TB chemotherapy, and 30 days after the start of anti-TB chemotherapy. The outcomes of patients lost to follow-up or dead were censored at the time of the last clinic visit or date of death. Otherwise, long-term outcome was evaluated on October 31, 1999.

Mycobacterial culture, identification, and drug susceptibility test

All cerebrospinal fluid (CSF) specimens were submitted for isolation of bacteria, mycobacteria, and fungi. Isolation of mycobacteria was performed by conventional methods [19]. The medium for primary mycobacterial isolation was Lowenstein-Jensen medium (BBL, Becton Dickinson, Sparks, MD, US) before 1996. After 1996, Middlebrook 7H11 agar (BBL, Becton Dickinson) was added. The BACTEC MGIT 960 system (Becton Dickinson) was added after July 1998. Standard biochemical methods were used to identify mycobacterial species [19].

The isolates of *M. tuberculosis* were tested for drug susceptibility using the modified proportion agar dilution method on 7H10 agar (BBL, Becton Dickinson). The following drugs were tested: isoniazid (0.2 and 1 μg/mL), rifampin (1 μg/mL), ethambutol (5 and 10 μg/mL), and streptomycin (2 and 10 μg/mL). Resistance was defined as a growth of over 1% of the colonies on drug-containing media, as compared with growth on drug-free control medium.

Case definition

The diagnosis of TB meningitis was classified as definite if culture of the CSF yielded *M. tuberculosis*. Diagnosis of TB meningitis was classified as presumptive if all of the following criteria were fulfilled: meningitis with subacute clinical course and serial examination of CSF compatible with TB meningitis (≥2 of the following 3 findings lasting for >3 weeks: pleocytosis with lymphocyte predominance, elevated protein level >45 mg/dL, and decreased glucose level <60 mg/dL); and negative CSF culture for virus, bacteria, and fungi, plus clinical response to anti-TB chemotherapy. In addition, the presence of extraneural involvement of TB plus symptoms or signs consistent with meningitis plus clinical response to anti-TB therapy was also considered presumptive diagnosis of TB meningitis. The diagnosis of cerebral tuberculoma was based on all of the following: the existence of TB meningitis, computed tomography (CT) revealing enhancing nodular lesions [20], lesions that cannot be explained by other etiology, and lesions responding to anti-TB chemotherapy. The diagnosis of cerebral TB abscess was based on all of the following: the existence of TB meningitis, CT revealing ring enhancement with central hypodense lesions [20], lesions that cannot be explained by other etiology, and lesions responding to anti-TB therapy. The diagnosis of TB spinal arachnoiditis was based on all of the following: the existence of TB meningitis, magnetic resonance imaging revealing thickened and enhancing spinal meninges [21], lesions that cannot by explained by other etiology, and lesions responding to anti-TB chemotherapy. The diagnosis of extraneural TB was based on either culture results from specimens of infection foci or tissue biopsy histology revealing granulomatous inflammation with caseous necrosis and Langerhans giant cells.

Neurologic status was classified into 3 clinical stages according to the criteria established by the BMRC [15]. In stage I, patients were fully conscious and rational with or without meningeal signs, but without focal neurologic signs. In stage II, patients were confused or had focal neurologic signs such as cranial nerve palsies or hemiparesis. In stage III, patients had either deep coma, delirium, dense hemiplegia, or paraplegia.

Morbidity was defined as having any neurologic sequelae directly related to TB meningitis at the final evaluation.

Statistical analysis

Statistical analysis was performed using Epi Info statistical software (Version 6.04B, CDC, Atlanta, GA, US). Categorical variables were compared using Fisher's probability test or chi-square test. A p value of less than 0.05 was considered significant.

Results

Over the 5-year study period, TB meningitis was diagnosed in 41 patients: 22 of these diagnoses were categorized as definite and 19 as presumptive TB meningitis (Table 1). The age of these patients ranged

Table 1. Laboratory data, diagnostic criteria, treatment, clinical staging, and long-term outcome of 41 patients with tuberculous meningitis

	Median (range)	No. of patients
Total WBC count in peripheral blood (n = 39[a]), /mm^3	8000 (2160-16180)	
Initial examination of CSF		
Pressure (n = 35[b]), mm H_2O	250 (70- 600)	
WBC count (n = 38[c]), /mm^3	210.5 (0-1760)	
Glucose level (n = 38), mg/dL	35 (7-101)	
Protein level (n = 38), mg/dL	173 (4-4100)	
Diagnostic classification		
Definite		22
Presumptive		19
Anti-TB chemotherapy		
Standard 4 combined therapy		30
Standard 4 combined therapy with steroid		9
No treatment[d]		2
Clinical staging at presentation		
Stage I		21
Stage II		18
Stage III		2
Clinical staging at start of anti-TB therapy (n = 39)		
Stage I		19
Stage II		18
Stage III		2
Clinical staging 30 days after anti-TB therapy (n = 38)		
Stage I		17
Stage II		20
Stage III		1
Long-term outcome		
No sequelae		14
Significant sequelae		23
Death directly due to TB meningitis		1
Death directly due to coinfection		3

Abbreviations: WBC = white blood cell; CSF = cerebrospinal fluid; TB = tuberculosis
[a]Missing data for 2 patients.
[b]Missing data for 6 patients.
[c]Missing data for 3 patients.
[d]Two patients died before anti-TB chemotherapy.

from 16 to 80 years (median, 40 years). The male/female ratio was 22:19. Drug susceptibility test results were available in 13 patients. All of the 13 isolates of *M. tuberculosis* were susceptible to isoniazid, rifampin, ethambutol, and streptomycin. All patients except 2 who died before using anti-TB chemotherapy were treated with the combination of isoniazid, rifampin, ethambutol, and pyrazinamide initially. The treatment duration of the surviving 37 patients ranged from 6 to 18 months with a median of 12 months.

Clinical features

Of the 41 patients, 17 had a history of a variety of underlying immunocompromising diseases, including diabetes mellitus in 5 patients, chronic renal failure in 3, acquired immunodeficiency syndrome in 5, alcoholism in 2, liver cirrhosis in 2, systemic lupus erythematosus in 2, and rheumatoid arthritis in one. Three patients had 2 underlying diseases. Nineteen patients, 12 with a definite diagnosis of TB meningitis and 7 with a presumptive diagnosis, had extraneural involvement of TB. This extraneural involvement was in the respiratory system in 17 patients (including 4 with miliary TB), gastrointestinal tract in 1, musculoskeletal system in 4, TB lymphadenitis in 3, hepatic TB in 1, splenic TB in 1, and renal TB in 1. Seven patients had 2 extraneural sites involved, and one had 3 sites involved. The leading presenting symptoms were fever (seen in 37 patients), headache (31), neck stiffness (28), consciousness change (11), and nausea and/or vomiting (11). Two patients had 2 of the above 5 symptoms, 27 patients had 3, 4 had 4, and 2 had 5. Twenty patients had at least one neurologic deficit at presentation, which included sphincter disturbance

(7 patients), hemiparesis (5), speech disorder (5), cranial nerves palsy (4), ataxia (3), coma (2), paraparesis (2), hearing disorder (2), and visual hallucination (2). Five patients had 2 neurologic deficits, 2 had 3, and one had 4.

The median duration from onset of symptoms to presentation was 14 days (range, 1-120 days) while that from the onset of symptoms to the start of anti-TB therapy was 18 days (range, 17-67 days) and that from presentation to the start of anti-TB therapy was 3 days (range, 20-34 days). Anti-TB chemotherapy had been begun 20 days prior to admission in a patient with tuberculous pleurisy who had poor adherence to the prescribed therapy at another hospital.

Most patients were in BMRC clinical stage I (21 patients) or II (18) at the time of presentation (Table 1). Only 2 patients were in stage III at the time of presentation. Two patients, both in stage II at presentation, died before the use of anti-TB chemotherapy; one died directly of TB meningitis and the other of nosocomial pneumonia. The clinical staging at the time of starting anti-TB chemotherapy was stage I in 19 patients, stage II in 18, and stage III in 2 (Table 1). Two patients progressed from stage I into stage II before anti-TB chemotherapy was started. One patient (in stage III) died 7 days after starting anti-TB chemotherapy. At 30 days after initiation of anti-TB chemotherapy, 17 patients were in stage I, 20 in stage II, and 1 in stage III. Two patients had progressed from stage I into stage II during this period.

Laboratory studies

The initial white blood cell counts of peripheral blood ranged from 2160 to 16 180 /mm^3 (median, 8000 /mm^3). Data on CSF examinations were available in 38 patients. Initial CSF studies showed opening pressures ranging from 70 to 600 mm H_2O (median, 250 mm H_2O; 10 patients had normal CSF pressures), white blood cell counts from 0 to 1760 /mm^3 (median, 211 /mm^3), glucose levels from 7 to 101 mg/dL (median, 35 mg/dL; 5 patients had normal glucose levels), and protein levels from 4 to 4100 mg/dL (median, 1730 mg/dL; 7 patients had normal protein levels) (Table 1). Pleocytosis was absent in the initial CSF study in only one patient, a 77-year-old woman without any underlying disease. However, her initial CSF profile revealed decreased glucose level (35 mg/dL) and elevated protein level (95 mg/dL). Furthermore, the second CSF examination taken 3 days later revealed pleocytosis up to 58 /mm^3 with predominance of lymphocytes. No patient had a totally normal CSF profile in the initial examination.

Except for 4 patients with normal radiologic findings, magnetic resonance imaging of the CNS at presentation showed enhancement of the basilar meninges in 33 patients, and thickened and enhanced spinal meninges in 2; CT revealed hydrocephalus in 13, ring or nodular enhancing lesions in 6, and cerebral infarction in 2. Four patients had 2 abnormal findings, 6 had 3, and 1 had 4.

Outcome

Among the 36 patients with complete medical records on change of daily body temperature, the duration from the commencement of anti-TB chemotherapy to defervescence ranged from 1 to 74 days (median, 14 days).

During the course of anti-TB therapy, 19 (48.7%) patients experienced new neurologic complications related to TB meningitis, including cerebral infarction (16 patients), spinal arachnoiditis (5), cerebral tuberculoma or abscess (4), exacerbated consciousness (4), tuberculous spondylitis (2), sphincter disorder (1), and abducens palsy (1). Six patients had 2 new complications, 2 patients had 3, and 2 patients had 4. Among them, 12 patients had a positive CSF culture for *M. tuberculosis*, 8 of whom had *M. tuberculosis* isolates tested for anti-TB susceptibility. These 8 isolates were all susceptible to isoniazid, rifampin, and ethambutol. Cerebral infarction, all in the middle cerebral artery territory, was the most common neurologic complication observed during anti-TB therapy. The duration from the start of anti-TB chemotherapy to the development of new neurologic complications ranged from 3 to 248 days (median, 39 days). Positive CSF culture for *M. tuberculosis*, clinical stage, age older than 65 years, abnormal imaging studies of the CNS other than meningeal enhancement, initial CSF protein levels, presence of underlying immunocompromising diseases, and use of steroids were not associated with the development of new neurologic complications (Table 2).

The median duration of follow-up for 39 patients who received anti-TB chemotherapy was 568 days (range, 85-1980 days). Two of them died of nosocomial pneumonia after anti-TB chemotherapy during their hospitalization; one was a previously healthy 27-year-old woman who presented with disseminated TB with involvement of the bone marrow, skin, lung, and CNS, and the other was a 34-year-old man with acquired immunodeficiency syndrome who presented with stage III TB meningitis. The follow-up durations of the 37 patients who survived were all over 180 days (range, 181-1980 days; median, 664 days).

Table 2. Development of new complications during anti-TB treatment based on various factors in 39 patients receiving anti-TB chemotherapy

Factor	No. of cases with new symptoms/ total no. of cases (%)	*p*
Positive CSF culture for *M. tuberculosis*		0.205
Yes	12/20 (60.0)	
No	7/19 (36.8)	
Stage I disease at the start of anti-TB treatment		0.752
Yes	10/19 (52.6)	
No	9/20 (40.9)	
Age over 65 years		1.000
Yes	5/10 (50.0)	
No	14/29 (48.3)	
Abnormal imaging study of the CNS[a]		0.205
Yes	12/20 (60.0)	
No	7/19 (36.8)	
Underlying disease		0.514
Yes	6/15 (40.0)	
No	13/24 (54.2)	
Initial steroid use		0.451
Yes	3/9 (33.3)	
No	16/30 (53.3)	
Total	19/39 (48.7)	

Abbreviations: CSF = cerebrospinal fluid; TB = tuberculosis; CNS = central nervous system
[a]Abnormal findings of image studies of the CNS did not include the basilar enhancement or brain swelling.

Twenty-three patients had significant neurologic sequelae. The overall morbidity and case fatality rates of 41 patients were 56.1% (23/41) and 9.8% (4/41), respectively. Among the 39 patients who received anti-TB chemotherapy, the morbidity and case fatality rates were 59% (23/39) and 5.1% (2/39), respectively.

Of the 39 patients receiving anti-TB chemotherapy, the morbidity and fatality rates in patients with positive CSF cultures for *M. tuberculosis* were 80% (16/20) and 5% (1/20), while those in patients with negative CSF culture for *M. tuberculosis* were 36.8% (7/19) and 5.3% (1/19), respectively (p=0.018 between these 2 groups).

To assess the predictive value of clinical stage, we compared the neurologic outcome and case fatality rate evaluated at different times in 39 patients who received anti-TB chemotherapy. Of the 21 patients in BMRC stage I at presentation, one patient died and 10 had neurologic sequelae after long-term follow-up (p=0.253 compared with patients in stage II plus III) (Table 3). Of the 19 patients in stage I at the start of anti-TB chemotherapy, none died but 9 had neurologic sequelae (p=0.06 compared with patients in stage II and III at the start of anti-TB chemotherapy). Of the 17 patients in stage I evaluated at 30 days after the initiation of anti-TB chemotherapy, 7 patients had neurologic sequelae and none died (p=0.034 compared with patients in stage II and III evaluated at 30 days after the initiation of anti-TB chemotherapy). Among the 21 patients in stage I at presentation, 4 progressed into stage II and 17 remained in stage I at 30 days after the initiation of anti-TB therapy. Three of these 4 patients had neurologic sequelae and one died. In comparison, among the other 17 patients, 7 had neurologic sequelae and 10 were cured without sequelae (p=0.025 by chi-square test).

The other factors assessed for predictive ability, including age older than 65 years, abnormal imaging studies of CNS other than meningeal enhancement, initial CSF protein levels, presence of underlying immunocompromising diseases, and use of steroids, did not influence the long-term neurologic outcome and fatality (Table 3).

Discussion

This study revealed that while TB meningitis in adult patients in an endemic area of TB was associated with a low case fatality rate, the prevalence of morbidity or neurologic sequelae remained high despite the administration of appropriate anti-TB therapy. Both neurologic evaluation at 30 days after initiation of anti-TB therapy and positive CSF culture for *M. tuberculosis* were predictive of long-term outcome of TB meningitis. In contrast, no correlation was found between long-term outcome and patients' age, CSF protein level, radiologic

Table 3. Morbidity and case fatality of 39 patients receiving anti-tuberculous chemotherapy based on various factors

Characteristic factor	No. of cases with morbidity/fatality/CWOS	*p*
Positive CSF culture for *M. tuberculosis*		0.018[a]
Yes	16/1/3	
No	7/1/11	
Stage I disease at admission		0.253
Yes	10/1/10	
No	13/1/4	
Stage I disease at the start of anti-TB therapy		0.060
Yes	9/0/10	
No	14/2/4	
Stage I disease 30 days after anti-TB therapy[b]		0.034[a]
Yes	7/0/10	
No	16/1/4	
Age over 65 years		0.385
Yes	7/0/2	
No	16/2/12	
Abnormal CNS image study[c]		0.201
Yes	14/1/5	
No	9/1/9	
Underlying disease		0.626
Yes	10/1/4	
No	13/1/10	
CSF protein level over 300 mg/dL[d]		0.597
Yes	8/1/2	
No	15/1/9	
Initial steroid use		0.462
Yes	6/1/2	
No	17/1/12	
Total	23/2/14	

Abbreviations: CWOS = cure without sequelae; CSF = cerebrospinal fluid; TB = tuberculosis; CNS = central nervous system
[a]The difference is statistically significant between the 2 groups.
[b]One patient died 7 days after starting anti-TB chemotherapy, leaving a total of 38 patients for analysis.
[c]The abnormal findings of imaging studies of the CNS did not include the basilar enhancement or brain swelling.
[d]Missing data of CSF protein values in 3 patients.

findings, use of steroids, or underlying diseases.

The case fatality rate (5.1%) of patients with TB meningitis who received modern anti-TB therapy in this study was lower than reported studies in the 1990s (7%-63%) [5-14]. It is difficult to compare previous studies with this study because the study populations, clinical stages at the start of treatment, treatment regimens, and timing of initiation of anti-TB therapy were different. However, the lower case fatality rate in this series may be partially related to the shorter duration from presentation of TB meningitis to initiation of appropriate anti-TB chemotherapy (median, 3 days) compared with previous study (6.7 days) [11].

Although the case fatality rate was lower, the morbidity rate in this study (58.5%) was much higher than those reported previously (8.3%-17.6%) [5-14]. The reasons for this discrepancy may be attributed to different study methods. Most previous studies did not give a clear description of outcome evaluation and some included only major sequelae [8]. In contrast, both minor and major neurologic complications and sequelae were evaluated in this study. In addition, because there was a lower fatality rate in this study compared with previous reports (5.1% vs 7%-63%) [5-14], more cases survived for a longer period of follow-up and thus contributed to the number of neurologic complications and sequelae noted in this series.

The role of concomitant prescription of steroids with anti-TB chemotherapy in the treatment of TB meningitis to reduce risk of neurologic complications and case fatality rate remains unclear [8,11,12,14,22-25]. However, lower morbidity and case fatality rates of TB meningitis have been attributed to the use of steroids in some studies [8]. Some authors even emphasized the value of steroid treatment for patients with stage II and III TB meningitis [26,27], because steroid might promote reduction of cerebral edema, vasculitis, and cranial nerve entrapment [28]. In this

study, we did not find the use of steroid to be a statistically significant factor associated with a better prognosis. However, the number of cases receiving steroids as a component of initial anti-TB treatment was too small (9 patients) in this study to adequately assess this relationship. It is possible that the high morbidity rate in this study might have been partly due to less use of steroid, compared with previous report in which both the low fatality rate and morbidity rate were considered results of the high frequency of steroid usage (96.6%) [8]. Determination of the role of steroid in the treatment of TB meningitis may require further well-designed, prospective studies.

Risk factors previously reported to be associated with a poor prognosis of TB meningitis included extreme age, clinical stage, hydrocephalus, positive CSF culture for *M. tuberculosis*, high initial CSF protein levels (>300 mg/dL), other underlying chronic medical diseases, and delayed treatment [11,12,29]. Although the clinical staging at the start of anti-TB chemotherapy has been reported to correlate well with outcome, the correlation was of borderline significance in this study (p=0.06). The duration from admission to the initiation of anti-TB chemotherapy did not significantly affect the outcome in this series, which might be attributed to the fact that early empirical use of anti-TB chemotherapy was common. Therefore, only 2 patients progressed from stage I disease at their presentation into stage II disease when anti-TB chemotherapy was started.

Positive CSF culture for *M. tuberculosis* and clinical stage II or III at 30 days after initiation of anti-TB chemotherapy were found to be the only 2 factors significantly associated with a worse long-term prognosis in this study. Positive CSF culture for *M. tuberculosis* may mean a higher concentration of *M. tuberculosis* in the CSF thus resulting in a poorer outcome. New neurologic complications may develop in patients with TB meningitis during the treatment period with effective anti-TB chemotherapy, necessitating repeat clinical or radiographic evaluation. Thus, reevaluation of the neurologic status at some period after starting anti-TB chemotherapy should be more representative of the long-term outcome. Those patients with disease progression from stage I into stage II evaluated between their presentation and 30 days after starting anti-TB chemotherapy were found to be associated with a worse prognosis compared with those without disease progression. There was no factor, including many clinical and laboratory parameters, found to be significantly associated with the progression of staging among these 21 patients (data not shown). This might be due to the small number of cases.

In this study, a high frequency (48.7%) of developing new neurologic complications during the course of anti-TB therapy was found. However, no significant factor associated with the development of new neurologic complications could be found. The duration from the initiation of anti-TB chemotherapy to the development of new neurologic complications ranged from 3 to 248 days, which is similar to those reported in other studies (10 days-18 months) [16-18].

Development of new neurologic complications during anti-TB therapy for TB meningitis can be due to use of ineffective or inappropriate anti-TB agents or to a paradoxical response. Complications due to ineffective or inappropriate agents were less likely in this series because most of the newly developed complications resolved or improved while the initial anti-TB chemotherapy was continued, after steroids were added, or after an operation was performed for symptomatic hydrocephalus. In addition, none of the bacterial isolates tested showed resistance to anti-TB agents. Paradoxical reaction during effective anti-TB chemotherapy is a well-known phenomenon [16-18]. It may be due to complex interaction between host immunity and the *M. tuberculosis*, and would subsided or improved with the continuation of initial anti-TB treatment or addition of steroid [16-18]. Thus, most of the newly developed neurologic complications in this series were considered to be caused by paradoxical response.

In conclusion, this study demonstrated that TB meningitis remains a disease associated with a high morbidity despite modern anti-TB chemotherapy, and that both advanced clinical stages at 30 days after starting anti-TB chemotherapy and positive CSF culture for *M. tuberculosis* were associated with a worse prognosis.

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