Tuberculous Meningitis: A Report of 60 Adult Cases

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ABSTRACT

Objective: *This was to evaluate the history, clinical and laboratory findings, outcome and prognosis of patients with tuberculous meningitis (TBM).*
Method: *Between 1998 and 2009, 60 patients with TBM were evaluated, retrospectively.*
Results: *Overall, 60 patients were selected, of which 33 (55%) were male. The patients' ages ranged from 14 to 62 years. In the majority of the patients, disease was in an advanced stage on admission (66% in stage III according to the British Research Council neurological criteria). The rate of complications was highest among patients in stages II and III with an overall mortality rate of 6.6% (n = 2 of stage II patients and n = 2 of stage III patients).*
Conclusions: *Earlier admission of the patients with TBM could provide better outcomes with regard to sequelae and mortality. Fatal cases presented with rapid deterioration and were refractory to treatment.*

Keywords: Mortality, sequelae, staging, tuberculous meningitis

Meningitis Tuberculosa: Reporte de 60 Casos Adultos

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RESUMEN

Objetivo: *El propósito de este trabajo fue evaluar la historia, los hallazgos clínicos y de laboratorio, la evolución, y la prognosis de pacientes con meningitis tuberculosa (MTB).*
Método: *Entre 1998 y 2009, se evaluaron 60 pacientes con TBM, retrospectivamente.*
Resultados: *En general, se seleccionaron 60 pacientes, de los cuales 33 (55%) fueron varones. La edad de los pacientes osciló de 14 a 62 años. En la mayoría de los pacientes, la enfermedad se encontraba en etapa avanzada al momento del ingreso (66% en la etapa III de acuerdo con los criterios neurológicos del Consejo Británico de Investigación). La tasa de complicaciones fue más alta entre los pacientes en las etapas II y III con una tasa de mortalidad general de 6.6% (n = 2 en los pacientes de etapa II y n = 2 en los pacientes de etapa III).*
Conclusiones: *El ingreso temprano de los pacientes con MTB podría proporcionar mejores resultados con respecto a las secuelas y la mortalidad. Los casos fatales se presentaron con deterioro rápido y fueron refractarios al tratamiento.*

Palabras claves: Mortalidad, secuelas, estadificación, meningitis tuberculosa

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INTRODUCTION

The World Health Organization (WHO) has reported that one-third of the world's population is infected with *Mycobacterium tuberculosis*. In 2009, nine million new cases of tuberculosis had been diagnosed and almost one million people died around the world. After the discovery of the Bacille Calmette-Guérin (BCG) vaccine, and the development of new antibiotics in the 1950s, the incidence of tuberculosis decreased. From 1995 to 2009, about 49 million people were treated for tuberculosis of which 41 million recovered (1). The recent increase of tuberculosis in developing and developed countries can in part be explained by the emergence of the HIV pandemic (2). According to the Ministry of Health, the incidence of tuberculosis in Turkey was 29 per 100 000 population in 2009. Of the 15 943 new cases with tuberculosis in Turkey in 2009, 36 cases were tuberculous meningitis. Incidence of tuberculosis has been

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steadily decreasing in Turkey over the last decade. The percentage of new tuberculous cases with multi-drug resistant tuberculosis (MDR-TB) was 0.4 and 56% of retreatment tuberculosis cases had MDR-TB (3). Tuberculous meningitis (TBM) composes 5−10% of all tuberculosis cases and is a very critical disease in terms of fatal outcome and permanent sequelae in spite of anti-tuberculosis treatment, requiring rapid diagnosis and treatment (4). Many prognostic factors for TBM have been reported, including age, the stage of the disease, level of consciousness, presence of extra-central nervous sys-tem tuberculosis, isolation of *Mycobacterium tuberculosis* from cerebrospinal fluid, pathologic biochemical findings of cerebrospinal fluid (CSF), hydrocephalus and cerebral in-farction (5). The diagnosis of TBM is based on the detection of acid-fast bacilli (AFB) in CSF smears, and, more com-monly, by the isolation of *M tuberculosis* from CSF cultures. A spiderweb clot in the collected CSF is suggestive of TBM, but is a rare finding. More than half of the cases of TBM cannot be confirmed with microbiological examination, and these patients are treated on the basis of clinical suspicion only.

In this study, we aimed to evaluate the impact of clinical and laboratory findings and disease staging on the outcome of patients with TBM.

SUBJECTS AND METHODS

Tuberculous meningitis patients, who were treated and followed up at the infectious diseases ward of the Ministry of Health Okmeydani Training and Research Hospital (OTRH) from 1998−2009, were included. Okmeydani Hospital is a tertiary hospital with an 800-bed capacity. Clinical, radiological and laboratory findings of all patients were evaluated, retrospectively. The diagnosis of TBM was based upon microbiological and biochemical analysis of CSF including white blood cell count, glucose and protein values. All patients had lumbar puncture twice, on admission and during treatment, to assess response to treatment. Each sample of CSF (5 ml of fluid) was centrifuged, and a portion of the deposit was examined by microscopy with Gram, Ehrlich-Ziehl-Neelsen (EZN), and India ink stains. The remaining deposit was cultured on blood and chocolate agar, and Lowenstein-Jensen medium (Merck Schuchardt OHG, Germany) as well as inoculated into BACTEC medium (Becton Dickinson Diagnostic Instruments Systems, Cockeysville, MD, USA) for some of the later cases when the BACTEC system be-came available. Data of the cases including anamnesis, phy-sical examination, laboratory (biochemistry and microbio-logy) and radiological findings were evaluated. The criteria that were taken into consideration in diagnosis of TBM were as follows:

- Age, symptom duration, pre-existing diseases or conditions, and exposure to a patient with tuberculosis, previous tuberculosis treatment, response to anti-tuberculosis treatment
- Demonstration of AFB with EZN method in CSF sediment or isolation of *Mycobacterium tuberculosis* from CSF by culture as described above
- Demonstration of AFB with EZN method in any clinical sample or isolation of *Mycobacterium tuberculosis* by culture of any clinical sample
- Manifestations of subacute meningitis (more than four days of signs of meningeal irritation with leukocytes more than 10 cells/mm^3 cells in CSF) and biochemical characteristics of CSF: protein greater than 1 g/L, glucose less than 45 mg/dL or CSF to blood glucose ratio of less than 0.5
- An active focus or the presence of sequelae of tuberculosis on chest X-ray, and presence of the findings of tuberculous meningitis on computed tomography (CT) or/and magnetic resonance imaging (MRI)
- The exclusion of other causes of meningitis (6−8)

Clinical staging: patients were divided into three stages according to the British Research Council neurological criteria (9):

Stage I: conscious, have non-specific symptoms, no neurological deficits.

Stage II: lethargy, behaviour changes, signs of meningeal irritation, minor neurological deficits (involvement of cranial nerves).

Stage III: stupor, coma, seizures, abnormal behaviours, severe neurological deficits.

All patients received standard treatment with isoniazid (INH) 300 mg/day, rifampicin (RIF) 600 mg/day, pyrazinamide (PZA) 2 g/day and ethambutol (ETB) 1.5 g/day. Streptomycin 1 g/day, intramuscularly and levofloxacin 1 g/day, orally were added to standard treatment in case of drug resistance or toxicity. Pyrazinamide and ETB were given for two months and in some patients, for three months. Isoniazid and RIF were given for 12 to 18 months. Stages II and III patients were treated with corticosteroids for a total of six weeks; dexamethasone was given intravenously for four weeks followed by two weeks of oral prednisolone. In addition, patients with culture-proven or suspected bacterial meningitis received 10 days of intravenous ceftriaxone 2 g twice per day. Patients judged to be at risk of HIV-1 infection were tested for HIV antibodies.

SPSS 13.0 (SPSS Inc, Chicago, IL) was used for statistical analyses. Patients' ages were described as range, median and mean ± standard deviation. Calculated percentages of variables were described without decimal. Statistical significance was determined at the 5% level. Continuous variables were compared by the two-sample *t*-test and dichotomous variables were compared by Fisher's exact test for two by two comparisons or Pearson χ^2 for greater than two responses. To study the independent effect of variables, we used multivariate logistic regression analysis. Logistic regression analysis was conducted to obtain unadjusted odds ratios and revealed as odds ratio (OR), 95% confidence interval (CI) and *p*-value. To identify the risk factors affect-

ing the development of TBM, related complications, sequelae and mortality were entered into a multivariate analysis using a logistic regression model (likelihood ratio test). Risk factors that reached statistical significance ($p < 0.05$) using a forward selection process remained in the model. Furthermore, we evaluated the correlation between stage according to the British Research Council neurological criteria (I–III) on admission, and variables such as duration of hospitalization, presence of MRI and CT findings on admission, positive EZN staining and positive Lowenstein Jensen culture of CSF, development of TBM related complications, sequelae and treatment related complications. Cerebrospinal fluid protein level and leukocyte counts were categorized to assess the relationship between inflammation level and outcome.

RESULTS

In total, 60 patients, mean age 30.06 ± 12.46 years and mean duration of symptoms 22.25 ± 20.22 days, were evaluated, retrospectively. Of those, 33 (55%) patients were male. Nine patients had pre-existing diseases or conditions such as hepatitis B (n = 1), diabetes mellitus (n = 4), hypertension (n = 1), migraine (n = 1), asthma (n = 1), chronic renal failure (n = 1), spontaneous abortion (n = 2) and history of cranial trauma (n = 2). Overall, only one patient was HIV positive. Mean hospitalization period was 18.23 ± 6.01 (range: 2−46) days. Onset of symptoms before admission was between 0 and 3 days in three (5%), 3−14 days in 27 patients (45%), 15−29 days in 14 (23%), 30−90 days in 16 (27%). The most commonly presented symptom was headache in 53 patients (88%). The most commonly examined sign was stiff neck in 53 patients (88%) [Table 1]. Stage status of the patients was 27 patients (45%) in Stage I, 29 (48%) in Stage II and four (7%) in Stage III. There was no significant correlation between stage of patients and other factors, such as duration of hospitalization, presence of MRI and CT findings at admission, positive EZN staining and positive Loewenstein Jensen culture of CSF, development of TBM related complications, sequelae and treatment related complications ($p > 0.05$). Cerebrospinal fluid examination showed lymphocyte predominance in 43 patients (86%), 0−200 leukocytes/mm^3 in 38 patients (67%), 201−500 leukocytes/mm^3 in 15 (26%), > 500 leukocytes/mm^3 in three (5%), protein ≥ 1 g/L in 33 patients (60%) and glucose < 45 mg/dL in 47 patients (85%). Ehrlich-Ziehl-Neelsen staining of CSF sediments demonstrated AFB in six patients (10%), and EZN staining of other samples (gluteal abscess and cranial stereorotactic biopsy) supported the TBM diagnosis in two patients. Cerebrospinal fluid cultures yielded *M tuberculosis* in 18 of the 60 patients (30%): in 10 patients (16%) with BACTEC and in eight patients (13%) with Lowenstein-Jensen medium, respectively (Table 2). Cerebrospinal fluid cultures yielded *M tuberculosis* in six patients with EZN staining positive. Of 18 patients whose CSF cultures yielded *M tuberculosis*, TBM related complications developed in seven (38%) patients, sequelae developed in five (27%) patients and two patients died. Of 38 patients whose CSF cultures did not yield organisms, TBM related complications developed in 16 (42%) patients, sequelae developed in nine (23%) patients and two patients died. There was no significant difference between patients who were culture positive and culture negative (p: 0.718, p: 0.823, respectively).

Table 1: Demographic data, clinical presentation and outcome of patients with tuberculous meningitis

		n (%)
Patient characteristics	Male sex	33 (55)
	Age, median (range), years	27.5 (14−62)
	Pre-existing diseases or conditions	9 (15)
	HIV infected patients	1 (1)
	Mean of symptom duration (days)	22.25 ± 20.22
	Previous pulmonary TB history	8 (13)
	Family history for TB	12 (20)
General symptoms and signs	Fever	42 (70)
	Headache	53 (88)
	Stiff neck	53 (88)
	Signs of meningeal irritation	19 (31)
	Nausea-vomiting	27 (45)
	Diplopia	9 (15)
	Unconscious	4 (6)
Neurological symptoms	Confusion	31 (51)
	Paralysis-paresis	11 (18)
	Cranial nerve paralysis	4 (6)
	Convulsions	1 (1)
Complications	Permanent neurologic sequelae	12 (20)
	Hydrocephalus	10 (16)
	Convulsion	3 (5)
	Syndrome of inappropriate antidiuretic hormone	9 (15)
	Myeloradiculopathy	8 (13)
	Visual disorders	6 (10)
Outcome	Full recovery	56 (94)
	Death	4 (6)

Table 2: Cerebrospinal fluid results in patients with tuberculous meningitis

	Normal range	n (%)
WCC: 0−200 × 10^6/L,	0−4	38 (63)
: 201−500 × 10^6/L		15 (25)
: > 501 × 10^6/L		3 (5)
CSF glucose: 45 < mg/dL,	60−90 mg/dL	47 (78)
CSF lymphocyte predominance n (%)		43 (71)
CSF protein > 1 g/L	15−45 mg/dL	33 (55)
Positive smear of CSF sediment (%)		6 (10)
Positive smear of other samples (%)		2 (3)
Positive mycobacterial culture (total)		18 (30)
with BACTEC		10 (16)
with Lowenstein-Jensen medium		8 (13)

WCC = white cell count, CSF = cerebrospinal fluid

The chest X-ray of 21 patients revealed miliary infiltration in seven (33%) patients, non-homogeneous infiltration in five (23%) patients, fibrotic parenchymal changes in five (23%) patients, cavitary lesion in three (14%) patients, and pleural effusion in one (4%) patient. Cranial MRI performed in 51 patients revealed leptomeningeal contrast enhancement in 19 (37%) patients and tuberculoma in 12 (23%) patients. Using cranial CT imaging, nine (34%) patients were found with hydrocephalus and two (7%) patients with tuberculoma (Table 3). Tuberculous meningitis related complications developed in eight of nine (88%) patients with CT findings and 16 of 34 (47%) patients with MRI findings. Sequelae developed in three of nine (33%) patients with CT findings, and seven of 34 (20%) patients with MRI findings. Four patients who died had CT and MRI findings. Due to drug resistance or toxicity, the standard therapy was extended by adding streptomycin in four patients, and levofloxacin in seven patients. Pyrazinamide and ETB were given for at least two months to all cases, but some patients received them for three months. Drug resistance was confirmed for ETB and INH, in one patient each. Due to hepatotoxicity (n = 15, 25%), drug related rash (n = 1, 1%) and optic neuritis (n = 1, 1%), treatment was modified or interrupted. All stage II and III patients (n = 33) received corticosteroid treatment. There was no side effect due to corticosteroids. Hydrocephalus occurred in 10 patients (16%) of whom four patients had hydrocephalus at admission and external shunt was placed in four patients (6%). The most frequent complication of TBM was permanent neurologic sequelae (n = 12, 20%), followed by hydrocephalus (n = 10), the syndrome of inappropriate antidiuretic hormone (n = 9), myeloradiculopathy (n = 8) and visual disorders (n = 6) [Table 1]. Mortality rate was 6.6% with four deaths: two (50%) of whom were admitted in stage II and the others were admitted in stage III. Sequelae rates with respect to duration of specific and non-specific symptoms before admission were 11% for 0−14 days, 14% for 15−29 days, and 36% for > 30 days. There was no correlation between mortality and gender, age, CSF leukocytes > 100×10^6/L, previous pulmonary tuberculosis history, paralysis on admission, duration of symptoms, pre-existing conditions and disease ($p > 0.05$). Duration of hospitalization of patients who died was less than 10 days (OR: 0.057; CI: 0.006, 0.553; $p < 0.032$). Development of TBM related complication was higher in patients with CSF protein > 1g/L (OR: 3.03; CI: 1.01, 9.1; $p < 0.042$), and CSF glucose < 30 mg/dL (OR: 4.61; CI: 1.37, 15.51; $p < 0.09$).

Table 3: Neuroradiological findings of the patients with tuberculous meningitis

Findings	CT (n = 26) n (%)	MR (n = 51) n (%)
Leptomeningeal enhancement	0 (0)	19 (37)
Tuberculoma	2 (7)	12 (23)
Hydrocephalus	9 (34)	6 (11)
Infarct	0 (0)	2 (3)

DISCUSSION

Tuberculous meningitis is the most severe form of tuberculosis and occurs due to reactivation of meningeal or subcortical focus (10). Mortality for untreated TBM is 100% (11). Tuberculous meningitis can be seen at all ages, but is more common in children age 0−5 years, and in adults between the ages of 25 and 45 years (12−14). Earlier studies conducted in Turkey reported that about 50% of the cases were between the ages of 15 and 30 years (12). In the present study, 53% of cases (n = 32) were between the ages of 15 and 30 years, and 40% (n = 24) were older than 30 years.

Tuberculous meningitis may have an acute presentation, but it is generally a disease that is slowly progressive. Sometimes it may present with cranial nerve deficits, or it may have a more indolent course, involving headache, meningeal signs, and/or altered mental status. Prodromal signs are usually non-specific, including headache, vomiting, photophobia, and prolonged fever more than two weeks. The duration of presenting symptoms may vary from one day to nine months. Due to the fact that many of the clinical findings are non-specific, the diagnosis of TBM can be difficult, but TBM should be considered in the presence of tuberculosis at a different focus or exposure to tuberculosis. A history of tuberculosis was reported for 8−12% of the adult TBM cases and it was found in 13% in this study (12−17). Twenty-seven cases were admitted to the hospital within the first two weeks after onset of clinical symptoms – a proportion that is similar to the one reported in the literature (17). The most commonly observed clinical symptoms and signs in our study, as well as in others, were fever, headache, confusion, nausea, vomiting and stiff neck (14, 18). Tuberculous meningitis typically affects the basal meninges, where it may involve cranial nerves and arteries as they traverse the subarachnoid space. Cranial nerve palsies and other focal signs are more common in TBM than in most other chronic forms of meningitis (19). The diagnosis of TBM cannot be made or excluded solely on the basis of clinical findings. Tuberculin testing is of limited value. Variable natural history and accompanying clinical features of TBM hinder the diagnosis.

The examination of CSF is essential for diagnosis of TBM. The cell count generally ranges from 0 to 1500/mm^3, the protein is elevated, and the CSF glucose is characteristically low and a lymphocytic predominance is usual (10). Still, exceptional cases of TBM might show normal glucose and protein levels and a predominance of polymorphonuclear leukocytes on CSF examination (13, 16). In the present study, 15% of cases had normal glucose and protein levels. Cerebrospinal fluid glucose was under 45 mg/dL in 11 of 12 TBM cases (91%) with permanent neurologic sequelae. Cerebrospinal fluid protein level could range

from 2−6 g/L in the case of spinal block or severe spinal arachnoiditis (20). Cerebrospinal fluid protein was 2 g/L in only one case that developed permanent paraplegia. Consistent with our results, TBM related complications were more likely to develop in patients with CSF protein > 1 g/L and glucose < 30 mg/dL. Culture and EZN staining of the cerebrospinal fluid are specific, but too insensitive to be used as the sole criteria for diagnosis. Culture and AFB positivity vary in different studies, from 9% to 90%, and 10% to 40%, respectively (16, 20, 21). In our study, culture and EZN staining positivity were as low as 30% and 10, respectively. The low number of bacteria in the CSF sediment, small amount of CSF sample, and being on tuberculosis treatment are possible reasons for not isolating *M tuberculosis* from CSF. In one study, stains of CSF sediment revealed AFB in only 37% of the samples on initial examination, but in 90% when fluids from four large-volume lumbar punctures were examined (22). While some studies reported that the CSF culture positivity was associated with worse prognosis, others could not corroborate these findings (22, 23). In our study, neurologic sequelae developed in five of 17 patients whose cultures were positive. Magnetic resonance imaging is superior to CT in identifying TBM related complications including cranial nerves and leptomeninges involvement, posterior cranial fossa lesions, granuloma, oedema surrounding tuberculoma and infarct (24, 25). In order of frequency, the MRI findings in our cases were leptomeningeal contrast en-hancement, tuberculoma, hydrocephalus, and infarct (24). In similar studies, the most commonly seen findings were des-cribed as tuberculoma, and arachnoiditis followed by hydro-cephalus and enhancement of basal meninges (22, 25, 26). The most common CT finding was hydrocephalus in nine patients (34%), four of whom needed an external shunt. Neurologic sequelae developed in three patients (33%) with hydrocephalus. Development of hydrocephalus was reported to be a poor prognostic sign by many studies (22, 26). The prevalence of HIV infection was very low in our study (only one patient). In Turkey, HIV prevalence is less than 0.1% (3). Although HIV seems to increase the risk of developing tuberculous meningitis, it does not alter the clinical and laboratory features of the disease (27). However, HIV infection alters the differential diagnosis in meningitic adults: opportunistic infection with unusual pathogens must be considered, in particular *Cryptococcus neoformans*, which can present subacutely in a similar way to tuberculous meningitis.

Treatment of TBM should begin as soon as possible *eg* when clinically suspected, because patient outcome is improved when therapy is started in the early stage of disease. Effective TB treatment is difficult, due to the unusual structure and chemical composition of the mycobacterial cell wall, which makes many antibiotics ineffective and hinders the entry of drugs (28). Drug-resistant TB is a public health issue in many developing countries, as treatment is longer and requires an extended combination of more expensive drugs. For TBM, treatment should begin with a combination of bactericidal drugs that penetrate into the CSF. The optimal duration of therapy for TBM has not been determined in a randomized, prospective, controlled trial. Treatment should be given for 12 months for intracranial tuberculoma, or tuberculoma with meningitis when the tuberculosis strain is sensitive to the antibiotics. Treatment should be extended to 18 months if the patient did not receive pyrazinamide during the first two months of therapy. If a patient has a multidrug-resistant strain of TBM, therapy is often extended to 24 months. It is also recommended that patients with active tuberculosis have directly observed therapy to ensure compliance, reduce the development of a resistant organism and monitor clinical response (29). While continuous therapy is important in regard to the clinical outcome, it could be a problem due to the high toxicity of the anti-tuberculosis drugs. When liver toxicity develops, the treatment should be stopped until toxicity resolves. The most controversial topic in the management of tuberculosis is the benefit of corticosteroids. Corticosteroids decrease tissue damage by preventing meningeal inflammation and interleukin secretion. Steroids are reported to be effective especially in patients with paradoxical reaction in improving disease outcome and clinical symptoms (29). Corticosteroids were given to all patients at stages II and III, in our study.

Mortality rates of TBM vary between 13 and 25% in other Turkish studies and 41% in similar studies from the United States of America (25, 30, 31). In countries where TB is endemic and which have a high HIV prevalence, mortality rates are significantly higher; *eg* 69% in South Africa (32). In our study, the overall mortality was 6.6%. Most of the patients with poor outcome died within the first 10 days of hospitalization. These findings once more stress the importance of early admission and treatment of patients with TBM. Tuberculous meningitis remains a serious disease in Turkey and other countries. The diagnosis of TBM remains difficult, even in a high-resource setting, as the currently available diagnostic tools lack sensitivity. To reduce morbidity and mortality, early diagnosis and prompt start of treatment are of utmost importance.

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