

# Evaluation of Twelve Patients with Tuberculous Meningitis

## Tüberküloz Menenjitli On İki Hastanın Değerlendirilmesi

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**ABSTRACT Objective:** To assess the presentation, diagnosis and treatment of patients with tuberculous meningitis (TM). **Material and Methods:** Clinical and laboratory findings of 12 patients with TM, followed-up between 2000 and 2004, were evaluated retrospectively. **Results:** Seven male and five female patients were enrolled in this study. The mean age of the patients was 34.5 years. Culture of cerebrospinal fluid (CSF) in 10 cases revealed *Mycobacterium tuberculosis*. None of the CSF samples was positive for acid-fast bacteria (AFB) by Ehrlich-Ziehl-Neelsen (EZN) staining. *M. tuberculosis* was also isolated from the sputum sample of one patient. Isoniazid (INH) resistance was detected in two isolates. The most frequent finding on cranial computerized tomography (CT) and magnetic resonance imaging (MRI) was tuberculoma. Hydrocephalus was observed in 4 cases. Five patients had pulmonary lesions on chest radiographs. One patient had cavitation on the right upper zone, one patient had bilateral apical hyperdensity, and three patients had miliary involvement. Liver toxicity due to anti-tuberculosis drugs developed in 2 patients. Paradoxical enlargement of tuberculomas was detected during therapy in one case. Cranial MRI appeared to be more sensitive than CT in detecting intracranial lesions of four patients. Three patients died and neurological sequelae developed in three patients. **Conclusion:** Early diagnosis and treatment is of major importance in TM, which is the most serious form of extrapulmonary tuberculosis. However, some problems such as drug toxicity and resistance, and occurrence of paradoxical response during follow up cause problems in treatment course.

**Key Words:** Tuberculosis, meningeal; technology, radiologic; therapy; drug resistance

**ÖZET Amaç:** Tüberküloz menenjitli (TM) hastaların tanı ve tedavilerinin değerlendirilmesi. **Gereç ve Yöntemler:** 2000-2004 yılları arasında TM tanısı ile takip edilen 12 hastanın klinik ve laboratuvar verileri retrospektif olarak değerlendirildi. **Bulgular:** Çalışmaya 7 erkek ve 5 kadın hasta dahil edildi. Hastaların yaş ortalaması 34.5 idi. On hastanın beyin omurilik sıvısı (BOS) kültüründe *Mycobacterium tuberculosis* üremesi oldu. Hastaların hiç birinin BOS örneğinin Ehrlich-Ziehl-Neelsen (EZN) yöntemi ile boyanarak incelenmesinde aside dirençli bakteri görülmedi. Bir hastada *M. tuberculosis* ayrıca balgam kültüründe de üredi. İki hastada üreyen *M. tuberculosis* isoniazide (INH) dirençli olarak saptandı. Kranial bilgisayarlı tomografi (BT) ve manyetik rezonans (MR) incelemesinde saptanan en sık bulgu tüberküloz idi. Dört hastada hidrocefali saptandı. Beş hastada akciğer grafisinde akciğerde lezyonlar görüldü. Bunlardan 1'si sağ üst alanda kavitasyon, 2'si her iki üst akciğer alanlarında yoğunluk artışı ve 3'ü miliyer tutulum şeklindeydi. İki hastada tüberküloz ilaçlarına karşı karaciğerde toksisite gelişti. Bir hastada tedavi sırasında tüberkülozda paradoks büyüme görüldü. Dört hastada intrakranial lezyonların tespit edilmesinde kranial MR incelemesinin BT'den daha duyarlı olduğu görüldü. Üç hasta öldü, 3 hastada nörolojik sekel kaldı. **Sonuç:** Ekstrapulmoner tüberkülozun en ciddi formu olan TM erken tanı ve tedavi çok önemlidir. Ancak izlem sırasında karşılaşılan ilaç toksisitesi ve direnci, paradoks yanıt gelişmesi gibi sorunlar tedavi seyrinde problemlere yol açmaktadır.

**Anahtar Kelimeler:** Tüberküloz menenjit; radyolojik bulgular; tedavi, ilaç direnci

**T**uberculosis remains as a major health problem and the World Health Organization (WHO) declared it a global emergency in 1993.<sup>1</sup> Central nervous system tuberculosis, the most threatening form of tuberculosis, accounts for approximately 5% of extra pulmonary tuberculosis.<sup>2</sup> TM is characterized as meningoencephalitis as it affects both the meninges and the brain parenchyma and its vasculature.<sup>3</sup> TM is usually caused by rupture of a subependymal tubercle into the subarachnoid space rather than direct hematogenous seeding.<sup>4</sup>

In this study, clinical, microbiological, and radiological features of twelve adult patients with TM who were hospitalized in Trakya University Hospital were evaluated and problems encountered during the diagnosis, follow up, and treatment were evaluated.

## STUDY POPULATION AND METHODS

Twelve adult patients hospitalized due to TM in Trakya University Medical Faculty Hospital between 2000 and 2004 were evaluated. The study was performed after permission from the Local Committee of Ethics in Science and according to the guidelines of the Helsinki II declaration. Diagnosis of TM was established when the presence of lymphocytic meningitis and at least one of the following findings were detected: 1) positive culture of CSF or other sterile body fluids or tissues for *Mycobacterium tuberculosis*; 2) AFB in CSF, sputum, sterile body fluid or tissue by EZN staining; 3) positive Mantoux reaction (after 10 units of tuberculin injection, skin induration of >10 mm or >15 mm if the patient has received BCG within the last five years) 4) household contacts or other substantial exposure to an individual with active tuberculosis; 5) radiological findings on cranial CT or MRI characteristic of *M. tuberculosis* including exudates in basal cisterns or Sylvian fissures, hydrocephalus, tuberculoma, infarcts, and gyral enhancement; and 6) clinical improvement with antituberculosis (anti-TB) therapy. Lymphocytic meningitis was considered if the CSF findings included the following: lymphocyte count

more than 10/mm<sup>3</sup>, protein level higher than 40 mg/dL, and CSF/serum glucose ratio lower than 0.6.<sup>5</sup>

Clinical conditions of the patients were classified into three stages according to the Medical Research Council Staging.<sup>6</sup> Stage I: patients with nonspecific symptoms, minimal signs of meningitis, no paresis, fully conscious, and in good general condition; stage II: patients with drowsiness or focal neurological signs; stage III: extremely ill, deep stupor or comatose patients.

The period between the onset of symptoms and initiation of anti-TB therapy was defined as the general period and the period between admission to the hospital and the initiation of anti-TB therapy was designated the interval period. Permanent neurological sequels were defined after 6 months. Management and duration of therapy were planned and were modified according to the stage of the patient, microbiological results and drug toxicity.

Clinical, laboratory, and radiological data were obtained for all patients. Cranial MRI and CT without using contrast material were performed in eleven patients. One patient did not give permission to perform radiological examination. Lumbar puncture was performed in all patients before starting therapy. CSF was examined for total and differential leukocyte counts, protein and glucose content. Direct Gram, Giemsa, EZN staining of CSF was performed for bacteriologic investigation. Specimens were cultured conventionally on Lowenstein-Jensen media and radiometrically (BACTEC 460TB system, BD biosciences). *M. tuberculosis* complex was differentiated from *Mycobacteria* other than tuberculosis using the BACTEC NAP (p-nitro- $\alpha$ -acetyl-amino- $\beta$ -hidroxy-propionophenone) test. Susceptibility testing for anti-TB drugs was performed by the BACTEC radiometric susceptibility assay. Antibiotic concentrations tested were 0.1  $\mu$ g/mL for INH, 2.0  $\mu$ g/mL for rifampin (RIF), 2.0  $\mu$ g/mL for streptomycin (SM), and 2.5  $\mu$ g/mL for ethambutol (ETB).<sup>7</sup>

## RESULTS

Twelve patients were enrolled in this study. Seven (58.3%) patients were male, and five (41.7%) were female. The mean age of the patients was 34.5 years (range, 18-72 years). The average duration of the general period was 12.5 days (range 3-25 days) and the average duration of the interval period was 2.3 days (range 0-12 days).

The most common symptoms on admission were headache, fever, nausea, and vomiting; the most frequent signs were neck stiffness, fever, and loss of consciousness (Table 1). One patient had convulsions on admission to the hospital and 4 had convulsions in the follow up period. Cranial nerve palsy was observed in 4 patients; one recovered with sequel. Involved cranial nerves were third, fourth, and sixth in one patient, only sixth in two patients, and only seventh in one patient. All aerobic cultures of the CSF were negative. EZN smear positivity was not detected in any of the CSF samples. *M. tuberculosis* was demonstrated in CSF by culture in 10 patients. The average time of culture positivity was 20.8 days (range 10-30 days). *M. tuberculosis* was detected in the culture of both sputum and CSF in one patient who was admitted to the hospital with stage III disease. Anti-TB drug susceptibility test was performed in all culture positive patients and INH resistance was detected in two.

Five patients had pulmonary lesions on chest radiographs. One patient had cavitation on the right upper zone, one had bilateral apical hyperdensity, and three had miliary involvement. While three patients had hydrocephalus on admission to hospital, hydrocephalus was detected in one patient on the fourth day of hospitalization. Ventriculoperitoneal shunt was performed in three patients with hydrocephalus. The cranial CT and MRI findings of 11 patients were presented in Table 2. Cranial MRI revealed a 0.5 cm nodule as well as perifocal edema in the right frontal lobe and millimetric nodules with contrast material enhancement in the basal occipital horn of the left side (Figure 1). Prednisolone in addition to anti-TB drugs was given to this patient. In the control cranial MRI after 3 weeks, enlargement of nodular le-

**TABLE 1:** Symptoms and signs of patients with tuberculous meningitis on admission to the hospital.

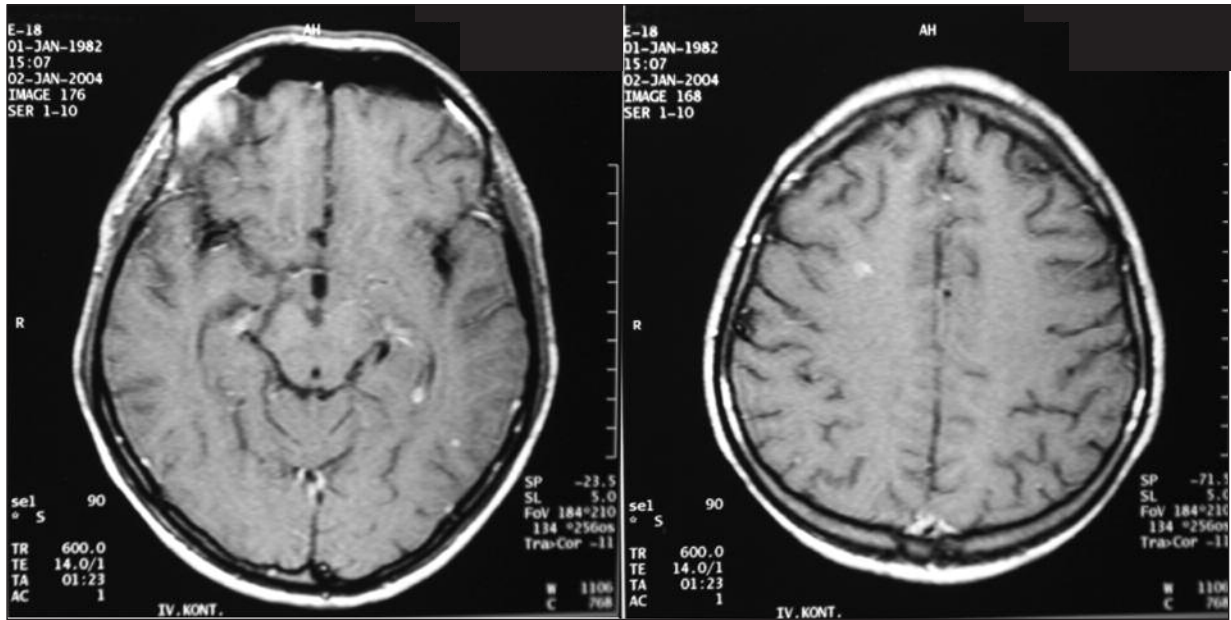
Symptoms and signs	Number (%)
<b>Symptoms</b>	
Headache	9 (75.0)
Nausea	9 (75.0)
Fever	8 (66.6)
Vomiting	7 (58.3)
Weakness	4 (33.3)
Lack of appetite	4 (33.3)
Double vision	1 (8.3)
Syncope	1 (8.3)
<b>Signs</b>	
Neck stiffness	10 (83.3)
Change of consciousness	5 (41.6)
Cranial nerve involvement	4 (33.3)
Paralysis/plegia	4 (33.3)
Nystagmus/ataxia	1 (8.3)
Convulsion	1 (8.3)

**TABLE 2:** Cranial CT and MRI findings.

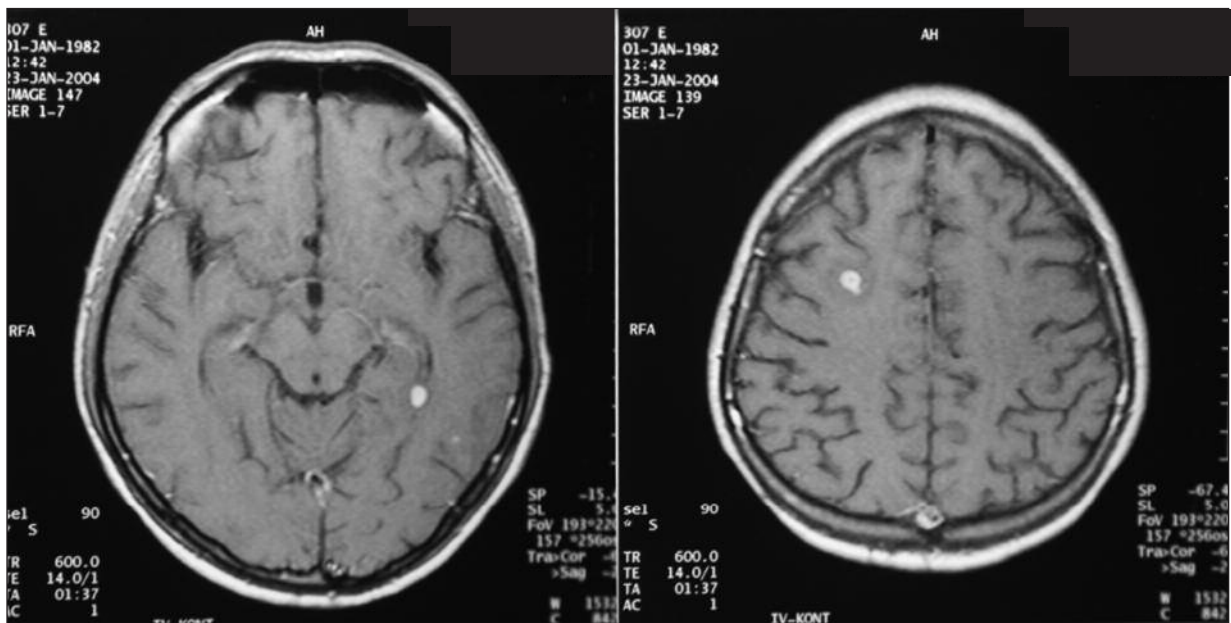
Finding	Cranial MRI (n: 11)	Cranial CT (n: 11)
Tuberculoma	6	2
Hydrocephalus	4	2
Basal meningitis	3	-
Infarction	1	1
Cerebritis	1	-

sions, increase in perifocal edema, and new millimetric nodules located sub cortically were detected in the left frontal, temporal, and both parietal lobes (Figure 2).

Liver toxicity due to anti-TB drugs developed in one patient. INH and RIF were stopped and treatment was maintained with pyrazinamide (PZA) and ETB. The patient was followed-up for 14 days and with liver enzymes within normal limits, treatment was continued with four drugs for 2 months and then with INH and RIF for an additional 10 months. In a patient with disseminated tuberculosis, treatment had to be stopped twice due to the liver toxicity of the drugs. Hearing loss and vision defect developed during treatment with INH, RIF, ETB, and SM. The treatment was continued with INH and PZA for 18 months. The clinical status of



**FIGURE 1:** Cranial MRI revealed a 0.5 cm nodule and perifocal edema in the right frontal lobe, and milimetric nodule with contrast material enhancement in the basal occipital horn of the left side.



**FIGURE 2:** Cranial MRI after 3 weeks, enlargement of nodular lesions, increase in perifocal edema and new milimetric nodules located subcortically were detected in the left frontal, temporal and both parietal lobes.

one patient admitted to the hospital with stage I disease deteriorated rapidly. On the fourth day of hospitalization, he had convulsions. Hydrocephaly and cerebral tuberculomas were detected and ventriculoperitoneal shunt was performed. The patient

died on the first day of treatment. CSF culture of this patient grew *M. tuberculosis* resistant to INH on the fourteenth day. The other patient with *M. tuberculosis* resistant to INH was given triple drug regimen for 12 months.



Three patients died during treatment. Two had stage III and one had stage I disease on admission to the hospital. Three patients improved clinically with neurological sequels; two had stage II and had stage III disease (Table 3).

## DISCUSSION

TM can occur at any age. In our study, the mean age of the patients was 34.5 and 50% was in the 15-25 age group. Other studies from Turkey reported similar results.<sup>5,8</sup>

The duration of the general period was 12.5 days and the interval period was 2.3 days in this study. Interval periods longer than 3 days were reported to be the most important factor associated with mortality by Verdon et al; on the other hand, other studies suggested that the long general period was more significant than the long interval period as a predisposing factor in the development of sequels.<sup>5,9,10</sup>

The most frequent symptoms on admission to the hospital were headache, nausea, vomiting, and fever; the most frequent signs were neck stiffness, fever, and consciousness changes. These findings were similar to data in other studies.<sup>5,8,11-13</sup>

High protein level in CSF was reported to be a statistically significant factor for poor prognosis by Hosoglu in Turkey and by another study from Qatar.<sup>12,14</sup> CSF analysis was performed in all of our patients on admission to the hospital and before treatment but statistical analysis could not be performed due to low number of patients in our study.

Culture positivity for *M. tuberculosis* was higher than in other reports. EZN staining of the CSF revealed no AFB in any of our patients while in 10 (83.3%) *M. tuberculosis* was isolated from CSF. In a previous study, culture and AFB positivity in CSF was 9.9% and 12.9% respectively.<sup>5</sup> In another

study, the rates were 21.4% and 7.1%.<sup>12</sup> The isolation rate of *M. tuberculosis* was 50% in the Qatar study.<sup>14</sup> In many clinical series, smear positivity for AFB in CSF by microscopy is <10% and the culture-positive rate varies from 25-70%.<sup>15,16</sup> Several studies reported that the CSF culture positivity was associated with worse prognosis.<sup>10,13</sup> Although culture positivity was high in our study, we could not evaluate its effect on prognosis due to the low number of patients. Two culture-negative clinically improved without sequel.

Cranial MRI is more sensitive than cranial CT in detecting the lesions below the level of brainstem and in the posterior fossa. CT may not detect tuberculoma. Cysticercosis, toxoplasmosis, some neoplasms, and other granulomatous diseases like sarcoidosis may be misdiagnosed as granuloma by cranial CT.<sup>17</sup> CT and MRI show hydrocephalus in 50-80%, cerebral infarctions in 25-30%, and perivascular edema and tuberculomas in 10-20% of the patients. The reported frequency of infarcts demonstrated by CT varies from 20% to 38% and their incidence is significantly higher in MRI than in CT. In general, all other lesions associated with TM are demonstrated better on MRI than on CT scan.<sup>18</sup> Different forms of lesions in TM were detected in the cranial MRI of 4 patients whose cranial CT images were normal. Although this finding may suggest the sensitivity of MRI in demonstrating TM lesions, the number of patients included in this study was not adequate to confirm this. This difference may also be due to not using contrast material for cranial CT. In our patients, the most frequent pathology detected on MRI was tuberculoma. This finding was followed by hydrocephalus and basal meningitis. In the study by Kilani et al including 122 cases, the most frequent pathologic findings on MRI were hydrocephalus, tuberculomas, leptomeningitis, infarction and brain abscess in following order.<sup>19</sup> In another study, the most frequent findings on cranial CT were hydrocephalus (47%), brain edema (11%) and tuberculoma (8%).<sup>8</sup>

Neurological sequels develop in elderly patients, infants with hydrocephalus, and patients whose diagnosis are established late.<sup>17</sup> Development of hydrocephalus was reported to be a poor

**TABLE 3:** Clinical staging and prognosis.

	Stage 1	Stage 2	Stage 3
Recovered (n)		6	
Had sequel (n)		2	1
Died (n)	1		2

prognostic sign by many studies.<sup>10,19</sup> In our study hydrocephalus developed in 4 patients; two died and two had neurological sequels. Hydrocephalus may be considered a prognostic factor in patients with TM.

The most controversial topic in the management of TM therapy is the benefit of corticosteroids. Corticosteroid is considered in the treatment due to its tissue injury decreasing effect by the preventing meningeal inflammation and interleukin secretion. In a prospective study, methylprednisolone was not effective in improving clinical outcome.<sup>20</sup> Steroids are reported to be effective especially in patients with paradoxical reaction in improving disease outcome and clinical symptoms.<sup>17</sup> Corticosteroid can suppress the host immunological processes against mycobacterial products, the mechanism which is considered to be responsible for the paradoxical reaction. In contrast, the number of tuberculomas increased in a case receiving corticosteroid treatment in the third week of therapy in our study. Tuberculomas were reported to develop in 23% of the corticosteroid administered cases in another study. Due to the absence of sufficient data on the rate of tuberculoma, it is difficult to conclude that corticosteroid therapy prevents development of tuberculoma.<sup>21</sup> Although studies attempted to control paradoxical growth of the cerebral mass lesion or cerebral edema, the effect of steroids on suppressing paradoxical response is not clear.<sup>22,23</sup>

Since continuous therapy is important in clinical improvement, anti-TB drug toxicity is a problem. When liver toxicity develops, the treatment should be stopped until toxicity resolves.<sup>5,8</sup> In our study, we had to interrupt treatment due to liver toxicity in two patients who developed neurological sequels.

Only a few studies were performed examining the relationship between different patterns of drug resistance and their effect on treatment response and outcome of TM. INH has an early potent bacte-

ricidal effect and its penetration to CSF is excellent; thus, TM caused by organisms resistant to this drug may be relatively harder to treat. INH and/or SM resistance probably has no significant detrimental impact on outcome because RIF-containing first-line antituberculosis drug regimen is sufficient for a good outcome while *M. tuberculosis* resistant to at least INH and RIF has a devastating effect on the outcome of TM.<sup>24</sup> In our study, we detected INH resistance in two cases; one died and the other was given triple drug regimen for 12 months.

Three patients had stage III disease on admission; two died and one developed neurological sequels. One out of eight stage II patients on admission had sequels, whereas the remaining seven patients were discharged from the hospital with clinical improvement. These results were in concordance with the findings in other studies, which stated that the stage of the patient was important for prognosis.<sup>12,25,26</sup> In another study, potential risk factors for mortality were reported as comatose state, delay in treatment and convulsions on admission to the hospital.<sup>8</sup>

In our study, three (25%) patients died and three (25%) patients had neurological sequels. Mortality rate was 21%, 23.3% and 13.1 % in three different studies reported from Turkey.<sup>8,11,27</sup>

In conclusion, early diagnosis and treatment is of major importance in TM, which is the most serious form of extrapulmonary tuberculosis. As it takes long time to isolate the bacteria in culture, it is better not to wait for diagnosis and to start treatment as soon as possible after a quick laboratory and radiological investigation period. One of the important reasons of unsuccessful treatment is the interruptions of treatment period because of drug toxicity. Moreover, drug resistance and occurrence of paradoxical response under treatment can prevent efficient treatment. Recognition of all these problems and the prescription of convenient treatment are very important.

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