Tuberculous Meningitis in Adults: A Review of 60 Cases

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Tuberculous meningitis (TBM) is a very serious disease. Early diagnosis and treatment is reduced mortality and morbidityrates in TBM. This study aimed to determine the main features of TBM cases. Retrospective case review study. All cases of TBM in adults tha to ccurred between 2006 and 2012, Atatürk University Hospital, were studied. The diagnosis of TBM was made using clinical, laboratory and neuroimaging features. The medical history, demographic data, admission symptoms, laboratory results, radiology findings, treatment and mortality rates were evaluated. In total, 60 cases of TBM were evaluated. There were 45% males and 55% females. The mean age presentation was 37.45 years. Headache, poor appetite, fever, sweating, cough and weight losspre dominant symptoms, while neck stiffness, mening ealirritation, blurred consciousness, hemiparesis and coma were the most frequent findings. Ten patients (16.7%), were in the first stage of the disease, 33 (55%) in the second, and 17 (28.3%) in the third. Mycobacterium tuberculosis grew in the cerebrospina lfluid (CSF) 20 (33.3%). Mycobacterium tuberculosis polymer a sechain reaction (PCR) was positivity 34 patients (56.7%). Totally, 11 patients (18.3%) died in thehospital. Were viewed the experience of our infectious diseases unit to define the current clinical presentation and prognosis of patients with advanced stages of TBM. The outcome of TBM is mainly determined by the clinical stage at admission. The advanced stage TBM is often associated with poorprognosis. We believe that early diagnosis and treatment of TBM cases may decrease morbidity and mortality significantly.

Key words: cerebrospinal fluid, headache, Mycobacterium tuberculosis, neck stiffness, tuberculous meningitis.

Tuberculosis (TB) is an infectious disease caused by the bacillus Mycobacterium tuberculosis. There were an estimated 12 million cases of TB in 2011. Global prevalence of tuberculosis is 170 cases per 100,000 individuals[1]. M. tuberculosis has infected one-third of the world's population[2,3]. Point prevalence rate in Turkey in 2010 was 24 per 100,000. A total of 5811 (35.1%) cases were identified as extrapulmonary[3]. Tuberculous meningitis is a rare but form of extrapulmonary tuberculosis (EPT), and the form with the highest mortality and morbidity rates. TBM is still a significant problem despite the development of radiological and microbiological diagnosis due to the increasing number of patients with HIV. When these patients cannot access treatment or are treated late, mortality and sequelae increase. TBM resembles HIV, and diagnosis based on clinical, radiological and laboratory findings is problematic. Early diagnosis and initiation of appropriate treatment are the keys to reducing

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mortality and morbidity in patients with TBM[2,5,6]. The purpose of this study was to evaluate clinical and laboratory findings, treatment and prognosis in patient investigated retrospectively at our clinic.

MATERIALS AND METHODS

This retrospective cohort study involved all adults diagnosed with TBM at a university hospital in the east of Turkey between 2006 and 2012. Ours is a 1500-bed tertiary university hospital providing health services to an urban area. It is also the major regional referral center. A standard case report form including demographic aspects, admission symptoms, radiology, laboratory and microbiological results, complications, treatment and outcome was used to collect data. Staging of TBM was assessed using Medical Research Council guidelines[7]. Medical Research Council staging was used to assess the severity of TBM. Under this system of staging, stage 1 patients are fully conscious and without focal neurological deficit; stage 2 patients may have altered consciousness or minor focal deficits such as hemiparesis or cranial nerve palsy; stage 3 patients are comatose or have severe focal deficits such as multiple cranial nerve palsy, hemiplegia and/or paraplegia.

In this study, diagnosis of TBM was based on presence of lymphocytic meningitis and at least one of the following[7].
1. Positive results for M. tuberculosis in cerebrospinal fluid (CSF), body fluids and tissues,
2. Positive microscopic acid fast bacilli in gastric aspirates, sputum, CSF and sterile body fluids,
3. Contact with an individual with active tuberculosis,
4. Clinical improvement with antituberculous therapy or
5. M. tuberculosis-specific exudates (basal cisterns or Sylvian fissures), tuberculoma, hydrocephalus, infarcts or gyral enhancement at cranial computed tomography (CCT) or magnetic resonance imaging (MRI).

The presence of lymphocytic meningitis, clinical picture (fever persisting for 2 weeks or more, headache, neck stiffness or altered mental status) and abnormal CSF findings (CSF pleocytosis with lymphocytic predominance, decreased CSF glucose and increased CSF protein) are indicative of TBM. Abnormal CSF findings are associated with a diagnosis of TBM in patients with chronic meningitis[8].

Statistical analyses

Statistical analyses were performed using SPSS version 20 (Chicago, IL). Univariate analysis of prognosis was based on the Chi-square test. A p value <0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics, radiological imaging and laboratory findings were recovered. Mean age of patients was 37.45 ± 15.97 years (range 13-71 years). Twenty-seven (45%) patients were male and 33 (55%) female (male/female ratio: 0.8). Mean duration of symptoms before admission was 26.45 ± 26.04 (2-150) days. Median length of hospitalization was 34.27 ± 19.69 (4-90) days. Eleven patients (18.3%) died and 49

Table 1. Symptomsandsigns on admission of 60 patients with tuberculous meningitis

	mean ±SD / n	(%)
Age (y) mean±SD	37.45±15.97	13-71
Symptomduration before admission	26,45±26.04	2-150
Neckstiffness	49	81.7%
Coma	10	16.7%
Paraplegia	8	13.3%
Cranialnervepalsy	14	23.3%
Fever	32	53.3%
Headache	56	93.3%
Vomiting	43	71.7%
Poorappetite	43	71.7%
Changes in personality	26	43.3%
Nightsweating	24	40.7%
Brudzinski'ssign	35	58.3%
Kern1ng test	32	53.3%
Hemiparesis	20	33.3%
Cough	20	33.3%
Weightloss	17	28.3%
Decreased level of consciousness	17	28.3%
Doublevision	9	15%

SD, standarddeviation

Table 2. Laboratoryfindings of TBM patients

Laboratory	mean ±SD
Blood Hemoglobin	13.37± 1.81
WBC count	10799.83± 4423.98
Platelets	295316.7±82421.3
Sodium (mmol/l)	132.80 ± 5.12
AST	30.30±18.15
ALT	32.73±37.87
Sugar (mg/dl)	124.70±45.58
Erythrocytesedimentation rate	37.67±30.71
CRP(0-5)	12.13±30.78

WBC, White cellcount; AST, aspartateaminotransferase; ALT, alaninetransaminase; CRP, C-reactive protein

Table 3. CSF findings

CSF	mean ±SD/n
CSF glucose	38.02±30.86
CSF chlorine	113.58±9.76
PMN (%)	296.17±720.25
CSF glucose 45›	14 (23.3%)
100‹	29 (48.3%)
100-500	18 (30%)
500›	13 (21.2%)
Lymphocyte (%)	119.83±119.03
Protein (mg/dl)	331.07±671.25
100›	46 (76.7%)
1000›	1 (1.7%)
Positive PCR	34 (56.7%)
Positivemycobacterialculture	20 (33.3%)
Positivesmear	3 (5%)
Positivepathology	2 (3.3%)

CSF, cerebrospinalfluid; PCR,PolymeraseChainReaction

Table 4. RadiologyFindings in 60 patients

	n	%
Leptomeningealenhancement	31	51.7
Pulmonarytuberculosis	21	35
Brain edema	21	35
Tuberculoma	21	35
Ýschemia, infarctions	20	33.3
Basalmeningitis	19	31.7
Small vesseldisease	17	28.3
Hydrocephaly	15	25
Mastoiditis	8	13.3
Normal	7	11.7

recovered (81.7%). The mean age of the six women and five men who died was 33.54. Admission symptoms of patients are shown in Table 1.

Clinical Findings

Ten (16.7) patients were in stage I, 33 (55%) were in stage II and 17 (28.3%) were in stage III. A statistically significant difference was determined among the clinical stages on admission in terms of prognosis ($p = 0.001$).

The most frequent admission symptoms were headache, vomiting and poor appetite. Almost all patients, 56 (93.3%), had headache, while 43 (71.7%) presented with vomiting and poor appetite. Fever was present in 32 (53.3%) patients. Neck stiffness was present in 49 (81.7%) patients at physical examination, changes in personality in 26 (43.3%), hemiparesis in 20 (33.3%), double vision in 9 (15%) and paraplegia in 8 (13.3%). The classic Brudzinski's sign was observed in 35 (58.3%). Coma on admission occurred in a minority of cases, 10 (16.7%). Seventeen (28.3%) patients were described as having a decreased level of consciousness. Cranial nerve palsy was determined in 14 (%23.3) patients. Sixth nerve palsy was determined in 7 (11.7%) patients and was the commonest form. This was followed by oculomotor nerve palsy in 3 (5%) patients, trochlear nerve palsy in 2 (3.3%) and facial nerve paralysis in 2 (3.3%)

Laboratory results

Sixty patients underwent lumbar puncture in the emergency room or our unit. CSF was analyzed in all patients. Mean leukocyte count in CSF was 296.17±720.25 (1-5400/mm3) and mean lymphocyte count 119.83±119.03 (1-530/mm3). Patients' laboratory parameters are shown in Table 2.

At investigation of CSF, lymphocyte count was below 50 in 38.3% of cases, between 50 and 100 in 43.3% and above 100 in 38.3%. Blood glucose levels were below 50 mg in 76.7% of patients. CSF glucose level was below 50 mg in 9 (81.8%) patients who died. CSF glucose to blood glucose ratio was over 0.6 in 4 (6.7%) patients and 0.3 or less in 56 (93.3%). Chlorine level was over 100 mmol/l in 54 (90%) cases and below 100 mmol/l in 6 (10%). Microbiological analysis of CSF revealed positive acid fast stain in 3 (5%) patients, positive culture in 20 (33.3%) patients, positive pathology 2 (3.3%) and positive PCR in 34 (56.7%) (Table 3).
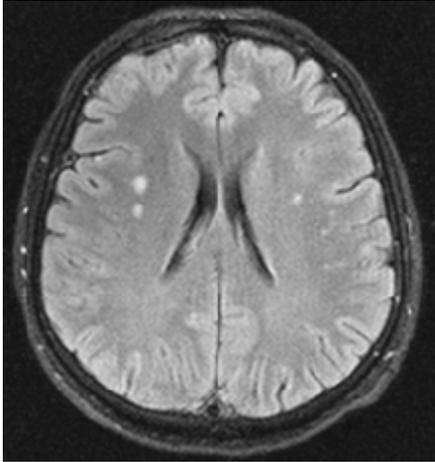
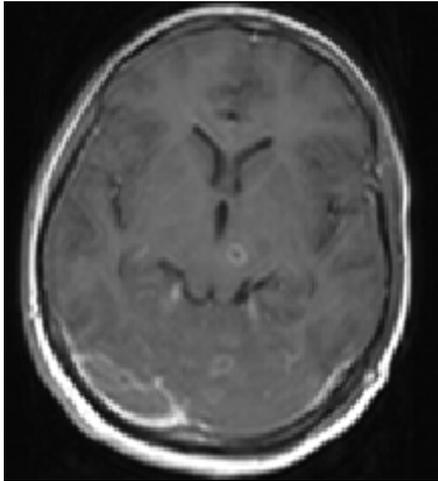**Fig. 1.** MRI showing no dular and ring-enhancing lesion in the brain parenchyma
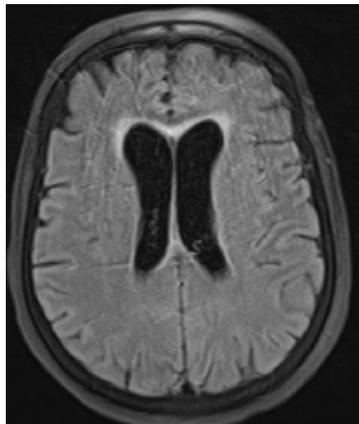

Fig. 2. MRI showing tuberculomas

Fig. 3. A head CT showing hydrocephalus

Radiological results

MRI and/or CCT were performed in all patients. These revealed cerebral edema in 21 (35%) cases, ischemic lesions in 20 (33.3%), small vessel disease in 17 (28.3%) and hydrocephalus in 15 (25%). Twenty-one (35%) patients had tuberculoma and 21 (35%) had pre-existing chest tuberculosis. Ten (16.6%) patients had miliary tuberculosis. Radiological features are shown in Table 4.

Treatment

Patients were treated with four drugs (isoniazid (INH), rifampicin (RFM), pyrazinamide (PZA) and ethambutol (EMB)) for 12-18 months. Selected patients received 24-month treatment. Following 2-3 months' treatment with the four-drug regimen, treatment continued with a two-drug regimen (INH and RPM). All patients received combination antibiotic therapy. INH 300 mg/day and RFM 600 mg/day were given for 12-18 months, PZD 1500 mg/day for 2 or 3 months and ETM 15-25 mg/kg per day or streptomycin (STM) 1 g daily for 1 month. All cases received steroid 1 mg/kg per day for 4-8 weeks.

DISCUSSION

The point prevalence rate reported in 2010 for Turkey was 24/100,000, and 5411 extra-pulmonary cases (35.1%) have been reported (4). Despite advances in radiological and microbiological diagnostic methods, TBM remains a significant health problem, particularly in conjunction with the increasing numbers of HIV-positive individuals. Delayed diagnosis is associated with increased mortality and severe sequelae. In this retrospective study, patients with TBM were assessed in terms of clinical, laboratory, therapeutic and prognostic factors.

Meningeal tuberculosis represents the most severe form of EPT, which comprises 5-10% of all TB cases. On the other hand, TBM accounts for approximately 1-1.3% of these extrapulmonary cases[8-12]. In a 7-year EPT study by Sevgi et al.[2] involving a total of 141 patients, the reported incidence of TBM was 23%.

Most of our patients were between 20 and 50 years of age (range: 13-71 years). Advanced age has previously been reported to be associated with poor prognosis[2,7,13,14]. There was no such

association in our study.

Due to men's more active life style, they are more often exposed to infection. The predominance of female patients (55%) in our series was explained on the basis of the economic and social conditions in Eastern Turkey, compared with a male to female ratio of 1.5 in the 2010 Report on the War on Tuberculosis, Turkey[4].

TBM may be associated with specific or non-specific clinical signs[6,9,11,15,16]. The most common presenting complaints include headache, nausea, vomiting, confusion and high fever[5,15]. Most of our patients were admitted with similar complaints to those listed above. The most common physical examination findings were neck stiffness, Kerning's and Brudzinski's signs and confusion[5,6,12]. Other manifestations such as diplopia and weak extremities were also observed.

Cranial nerve palsy has been reported in approximately 20% to 30% of cases[16-19]. Ho_olu et al.[7] established that the presence of cranial nerve palsy (7%) was an independent predictor. Moghtaderi et al.[20] observed cranial nerve palsy in 35.5% of their cases. Multivariate logistic regression analyses revealed a positive predictive value for this parameter (odds ratio 1.98). Cranial nerve palsies were determined at a level of 23.3% in our patients. The 6th cranial nerve was the most commonly involved nerve (11.7%) followed by the 3rd (5%), and 4th and 7th cranial nerves (3.3%).

CSF changes included pressure increase, elevated cell counts and protein content and decreased glucose and chlorides (8,12). Microbiological diagnostic methods (direct observation and growth of the causative agent) are the gold standard for diagnosis of TBM (8,11,12,14). In our cases, acid-resistant bacilli (ARB) were observed in 5% of cases with EZN staining of CSF. This staining rate was lower than the figures of 9.5% previously reported by Christensen et al. (21) and 19.6% by Sütla_ et al. (19), but was higher than that reported by Gunawardhana et al. (17) (0%). A relatively lower rate of ARB detection was probably associated with inadequate CSF sampling, inappropriate preparation techniques, and insufficient numbers and times of microscopic examination. TB bacilli can be grown in culture medium in 45-90% of cases (5,16,21). The figures reported by Yaram1_ et al. (18), Pasco (8), Sütla_ et al. (19), Gunawardhana et

al. (17), Pehlivanolu et al. (22), and Christensen et al. (21) were 1%, 4.4%, 1%, 21%, 39.9%, and 74%, respectively. In our study, growth in CSF cultures was observed in 20 patients (33.3%). Our growth rate is lower than that in some previous reports due to issues associated with the quality of CSF samples and the methods used. This may be due to the lack of a quality TB laboratory in our hospital.

Nucleic acid amplification (NAA) techniques have also been suggested for the diagnosis of TBM. Polymerase chain reaction (PCR) for diagnosis of TBM has a sensitivity of 56% and specificity of 98% (12,15,22,23). Several guidelines have proposed that PCR can be used for the diagnosis of TBM. This is a quick, but expensive method requiring relatively advanced technical laboratory equipment. Such NAA tests cannot therefore replace the current standard microbiological procedures on a routine basis for the time being, although combined use is recommended for diagnosis and differential diagnosis of TBM (16). Gunawardhana et al. (17) reported PCR polymerase chain reaction positivity in 31% of cases. Microbiological analysis of CSF revealed positive TB PCR in 34 (56.7%) of our patients.

Factors suggesting a poor prognosis include age over 40 years, high CSF protein, CSF cell count, seizures, stroke, cranial nerve palsy, lactate levels, hyponatremia, a GCS below 8, co-infection with HIV stage III, use of TNF alpha, cancer, and absence of headaches (7,13,14,16,24). BCG positivity has been shown to be a preventive factor against mortality. Tuberculin skin test negativity is a significant factor in mortality (9,18). The most important prognostic parameter in our study was the stage of the disease, while early diagnosis and early start of treatment were other important parameters. The mortality rate in HIV negative adults is 25%, and 67% in HIV positive patients [16]. In some previous reports, HIV seropositivitywas found to have no effect on mortality (13,19,25). All patients were HIV seronegative. At the time of diagnosis, approximately 85% of our patients were at stage II or III. This was probably due to a number of factors, including non-specific clinical presentation, socioeconomic difficulties, and delayed diagnosis.

Imaging modalities play a significant role in the early diagnosis of TBM as well as in

assessing the feasibility of surgical intervention. Ho_olu et al.[25] suggested that abnormal CCT findings were associated with poor prognosis. In a study involving pediatric cases of TBM, Kelekçi et al.[9] observed hydrocephalus in 68.6% of subjects, shunt procedure being required in 45.9%. Similarly, Yaram1_ et al.[18] examined a group of pediatric patients with TBM in which 80% developed hydrocephalus, mostly requiring surgery. Pehlivanolu et al.[22] reported tuberculomas, basal meningitis, and hydrocephalus in 36.6%, 26.9%, and 20.9% of their cases, respectively. In the study by Ho_olu et al.[7] detected hydrocephalus, tuberculomas, cerebral edema, and miliary appearance in 46%, 12%, 11%, and 8% of their study subjects, respectively. Due to as yet unknown reasons, paradoxical tuberculomas may tend to grow larger despite successful treatment. These patients require close monitoring (10). Two of our patients exhibited this clinical picture. Radiology revealed leptomeningeal staining in 51.7% of patients, tuberculomas and edema in 35%, ischemia and infarcts in 33.3%, small vessel disease in 28.3%, and hydrocephalus in 25%. Lung involvement was detected (using X-ray and microbiological data) in 35% of subjects. Miliary appearance was present in 16.6% of cases, which is lower than the level reported in some previous studies. This difference may reflect the use of both CCT and MRI by a radiologist with particular expertise in this field.

Additionally, early therapy can minimize the incidence of neurological sequelae and death. Despite the use of anti-tuberculous medications, mortality rates are generally high, and the disease is associated with significant sequelae. The initial choice of therapy should include isoniazid, rifampicin, pyrazinamide or ethambutol[1,4,5,14,23]. Longer-term treatments have been reported to result in lower relapse and mortality rates[26]. In our patients, four anti-tuberculous agents were administered for at least 12 to 18 months, and up to 24 months in some cases. Adjunctive steroid reduces mortality from tuberculous meningitis, but how it achieves this effect is unclear[3]. Regardless of the stage of the disease, dexamethasone was given to all patients in the first five days of treatment, followed by prednisolone for one month.

Figures for mortality in studies by Hoolu et al.[25], Sütla et al.[19], Yaram et al.[18] and Hoolu et al.[7] were 43.5%, 27.8%, 23%, and 23%, respectively. The lower rate of mortality in our study (18.3%) compared to other figures from Turkey may be associated with early commencement of treatment, prolonged and uninterrupted treatment, use of steroids and low rates of resistance. In this regard, the study by Sevgi et al.'s[2] study represents an exception in that respect, with a lower mortality level (9%). The mortality rates from studies by Gunawardhana et al.[17], Christensen et al.[21], Kurien et al.[24] and Ya_ar et al.[27] were 27%, 19%, 11.8% and 17%, respectively.

There are several limitations to our study:
a)   Its retrospective nature
b)   Retrieval of patient information from patient files and digital records
c)   Relative insufficiency of microbiologically positive results
d)   Lack of long-term follow-up data for some patients
d)   Lack of vaccination scar and PPD data for some patients and
e)   Lack of information in terms of close family contact in some patient files.

CONCLUSION

TBM is the most severe form of extra pulmonary tuberculosis. Unfortunately, TBM is generally diagnosed at a late stage due to its non-specific signs and symptoms, resulting in a high rate of morbidity and mortality. Although direct microbiological examination and growth represent the gold standard for diagnosis, the importance of anamnesis and imaging studies cannot be denied. Early diagnosis emerged as the most important prognostic factor in our study. However, methods that allow definitive early diagnosis are still needed. Therefore, before TBM is diagnosed, empirical anti-tuberculosis therapy should be initiated in all cases of suspected TBM.

ACKNOWLEDGMENTS

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