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Evaluation of radiological findings in 160 adult patients with tuberculous meningitis

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Aim: To evaluate the radiological findings of 160 adult patients with tuberculous meningitis (TBM).

Materials and methods: Using a standard data collection form, 160 patients with TBM who had been followed for 11 years were assessed retrospectively. Cranial imaging results were obtained by computed tomography (CT) and magnetic resonance imaging (MRI), and pulmonary findings were obtained by chest X-ray and CT. Tuberculomas were assessed with a nominal tuberculoma classification index (TCI) scale.

Results: Of the 160 patients, 80 were males and the mean age was 32.18 ± 13.62 years (range: 14-78). On admission, 84% were in stages II or III; 27 of them died (17%) and 20 had neurological sequelae (13%). Active pulmonary tuberculosis (TB) presence was significantly higher in the deceased patients than in the survivors (P = 0.019). Tuberculoma (37%), basal meningitis (27%), and hydrocephalus (21%) were the most frequent signs found in the cranial CT or MRI scans, and tuberculomas were mostly multiple and <1 cm according to the TCI.

Conclusion: Neuroimaging techniques are useful parameters in the early diagnosis of TBM. In particular, MRI provides specific findings for defining TBM, such as tuberculoma, basal meningitis, or hydrocephalus. The TCI may be useful in defining, following, and comparing the features of tuberculomas as a standard nominal scale.

Key words: Tuberculous meningitis, tuberculosis, MRI, pulmonary tuberculosis, M. tuberculosis, tuberculoma, hydrocephalus

Tüberküloz menenjitli 160 erişkin olguda radyolojik bulguların değerlendirilmesi

Amaç: Bu çalışma, tüberküloz menenjitli (TBM) 160 erişkin olgunun radyolojik bulgularını değerlendirmeyi amaçlamaktadır.

Yöntem ve gereç: Onbir yıllık dönemde izlenen TBMli 160 olgu, standart veri formu kullanılarak retrospektif olarak değerlendirildi. Kranyal görüntülemeler, komputerize tomografi (CT) ve manyetik rezonans inceleme (MRI) ile, pulmoner bulgular ise akciğer filmi ve tomografisi ile saptandı. Tüberkülomlar, "Tüberkülom Sınıflama Indeksi" ile derecelendirildi.

Bulgular: Yaş ortalaması 32,18 ± 13,62 (dağılımı 14-78) olan 160 hastanın 80'i erkekti. Hastaneye başvurduklarında olguların % 84'ü Evre II ve III idi. Olguların 27'si (% 17) öldü ve 20'sinde (% 13) nörolojik sekel gelişti. Aktif pulmoner tüberküloz oranı, ölen grupta sağ kalanlara göre anlamlı olarak yüksekti (P = 0,019). Kranyal CT ve MRI'da en sık rastlanan bulgular tüberkülom (% 37), bazal menenjit (% 27) ve hidrosefali (% 21) idi. TCI skalasına göre tüberkülomların çoğu multipl ve <1 cm idi.

Sonuç: Nörolojik görüntüleme yöntemleri, TBM'nin erken dönemde tanısında kullanışlı yöntemlerdir. Özellikle kranyal MRI; tüberkülom, bazal menenjit, hidrosefali gibi tüberküloza özgü bulguların tespitine imkan verir. TCI, tüberkülomların özelliklerinin karşılaştırılması, takibi ve tanımında standart bir skala olarak faydalı olabilir.

Anahtar sözcükler: Tüberküloz menenjit, tüberküloz, MRI, pulmoner tüberküloz, M. tuberculosis, tüberkülom, hidrosefali

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Introduction

Tuberculous meningitis (TBM) is the most important and dangerous form of extrapulmonary tuberculosis (EPTB). Despite effective antituberculous therapy, high mortality rates and neurological deficits are common in patients with TBM (1-3).

TBM is characterized by necrotizing granulomatous inflammatory response affecting the midbrain and hindbrain. The specific lesions of the disease are granulomatous lesions, which form the tuberculomas; inflammatory exudates on basal cisterns obstructing the flow of cerebrospinal fluid (CSF) and causing hydrocephalus; and adhesions that compromise obliterative vasculitis and result in infarcts (4). These characteristic lesions may be shown by neuroimaging techniques and may be useful for diagnosis of TBM if available in stage I (5).

Unfortunately, the early and exact diagnosis of TBM still remains difficult due to time-consuming definitive microbiological procedures. Coexistence of extraneural tuberculosis (TB), which may be a clue to central nervous system (CNS) TB, is reported among 50%-70% of TBM cases (6,7). The increasing use of computed tomography (CT) and magnetic resonance imaging (MRI), which provide TBM-related signs such as basal enhancement, hydrocephalus, or tuberculoma, will contribute both to the diagnosis and prediction of poor outcomes of the disease, in addition to the clinical and CSF findings (2,5,6,8-15).

This study presents the radiological findings of patients with TBM; the diagnosis, management, and follow-up of 160 TBM patients were done in a single center.

Materials and methods

Patient population and setting

İstanbul is the largest city in Turkey and has high rates of TB. Most patients with EPTB, especially TBM, receive care at the Haseki Training and Research Hospital (HTRH), a 550-bed tertiary referral center hospital. Included in this study were 160 patients, aged >14 years, who were diagnosed with TBM at the HTRH between January 1998 and March 2009. Of these patients, 7 were excluded due to incomplete data. Using a standard data collection form, data on clinical, radiological, and laboratory findings and 6-month outcomes were abstracted. Data were obtained from patients' hospital files, discharge summaries, and out-patient records, retrospectively. Ethics approval was not required for this retrospective study.

Definitions

The patients with lymphocytic meningitis, fever and headache with nuchal rigidity or altered sensorium for more than 2 weeks, pleocytosis, and protein increase and glucose decrease in the CSF were considered as having TBM when they also met at least one of the following criteria: 1) a positive culture of CSF or body fluids or tissues for *Mycobacterium tuberculosis*; 2) positive microscopy for acid-fast bacilli or polymerase chain reaction for *M. tuberculosis* from CSF, sputum, or other body fluids or tissues; 3) close contact with a person with active pulmonary TB; 4) radiological findings from a cranial CT/MRI scan or chest X-ray; or 5) clinical response to antituberculous therapy (2,4,7,13,14). Patients without these features were excluded.

Evaluation

The clinical stage of the patients was assessed according to the British Medical Research Council criteria: in stage I, patients with no neurological findings; in stage II, patients with focal neurological signs; and in stage III, patients with severe neurological findings or coma (16).

An urgent CT brain scan was done before or after the first lumbar puncture for all of the available patients on admission, and a contrast-enhanced CT or MRI scan of the brain was performed within 72 h. A follow-up CT or MRI scan was done if clinical deterioration or progressive hydrocephalus were found. Intravenous gadolinium-based contrast agents were used for MRI. Hydrocephalus, basal enhancement, tuberculoma, and infarcts were evaluated. Tuberculomas were also evaluated and classified according to their location, number, size, and presence of caseous necrosis. This nominal scale was named the tuberculoma classification index (TCI). Chest X-rays obtained from 101 of the 160 patients were assessed according to the presence of miliary shadowing, active tuberculous infiltration, and cavitary or fibrous sequelae lesions.

Results

The radiological findings of 160 patients (the male-to-female ratio was 1:1) with TBM, who were diagnosed and treated during an 11-year period, were evaluated retrospectively. Of these patients, 3 were pregnant and 1 had given birth 4 months earlier. Only 1 of the 160 patients had human immunodeficiency virus (HIV) infection. The mean age was 32.18 ± 13.62 years. Patients' demographic, clinical, laboratory, and cranial imaging features are summarized in Table 1.

Clinical and laboratory findings

Of the 160 patients, 84% were in stage II or stage III. Headache, fever, and vomiting were the most common symptoms, while neck rigidity, fever, and altered sensorium were the most common findings. The duration of symptoms before diagnosis ranged between 2 and 365 days. Concomitant extrameningeal TB was found in 38% of the patients, 27% had a previous history of TB, and 19% had a family history of TB. *M. tuberculosis* was isolated from the CSF samples of 59 of 148 patients (40%). Underlying comorbidities such as diabetes mellitus, trauma, and malignancy were detected in 37 patients (23%).

Radiological findings

All of the patients, except for 26, were evaluated with neuroimaging techniques in addition to the clinical and laboratory findings: 32 with a CT scan, 27 both with CT and MRI scans, and 75 with only an MRI scan. Tuberculoma was observed in 49 patients (37%), basal meningitis in 36 (27%), hydrocephalus in 28 (21%), and infarct/ischemia in 12 (9%) (Figure 1).

Tuberculoma was detected in 42 patients on admission, and in 7, it developed during the therapy as a paradoxical reaction. In Table 2, data for 49 patients with tuberculomas, evaluated according to the TCI, are summarized. During the follow-up period, radiological response to 12-18 months of antituberculous therapy (ATT) was evaluated in ≥90% of the patients with tuberculomas.

Basal meningitis (27%) and leptomeningeal involvement (25%) were detected in 70 of the patients. All of the radiological signs obtained by cranial CT or MRI are summarized in Table 3, and the differences between the CT and MRI signs are given in Table 4.

Table 1. Patients' demographic, clinical, and laboratory features.

Age: mean ± SD		32.18 ± 13.62
Age: range		14-78
Median duration of TBM		39 days
Duration of TBM: range		2-365 days
Sex		**n (%)**
Male		80 (50)
Female		80 (50)
Complaint duration		
<1 week		11 (7)
1-3 weeks		91 (57)
>3 weeks		58 (36)
Stage		
I		26 (16)
II		101 (63)
III		33 (21)
Clinical findings		
Headache		138 (86.3)
Fever		110 (69.2)
Nausea-vomiting		102 (63.8)
Asthenia-anorexia		65 (40.6)
Personality change		44 (27.5)
Weight loss		42 (26.3)
Night sweating		37 (23.1)
Neck rigidity		141 (88.1)
Meningeal irritation sign		59 (36.9)
Altered sensorium		95 (59.4)
Cranial nerve palsy		38 (23.8)
Coma		33 (20.6)
Convulsion		25 (15.6)
Plegia-paresis		24 (15)
Gait abnormality		21 (13.1)
Laboratory findings		
CSF WBC count/mm^3, n: 148	<100	47 (31.8)
	100-500	86 (58.1)
	>500	15 (10.1)
CSF/blood glucose ratio, n: 148	<0.60	140 (94.6)
	≤0.30	81 (54.7)
CSF protein level mg/dL, n: 148	<40	13 (8.8)
	40-150	74 (50)
Positivity of culture in CSF		59 (39.9)

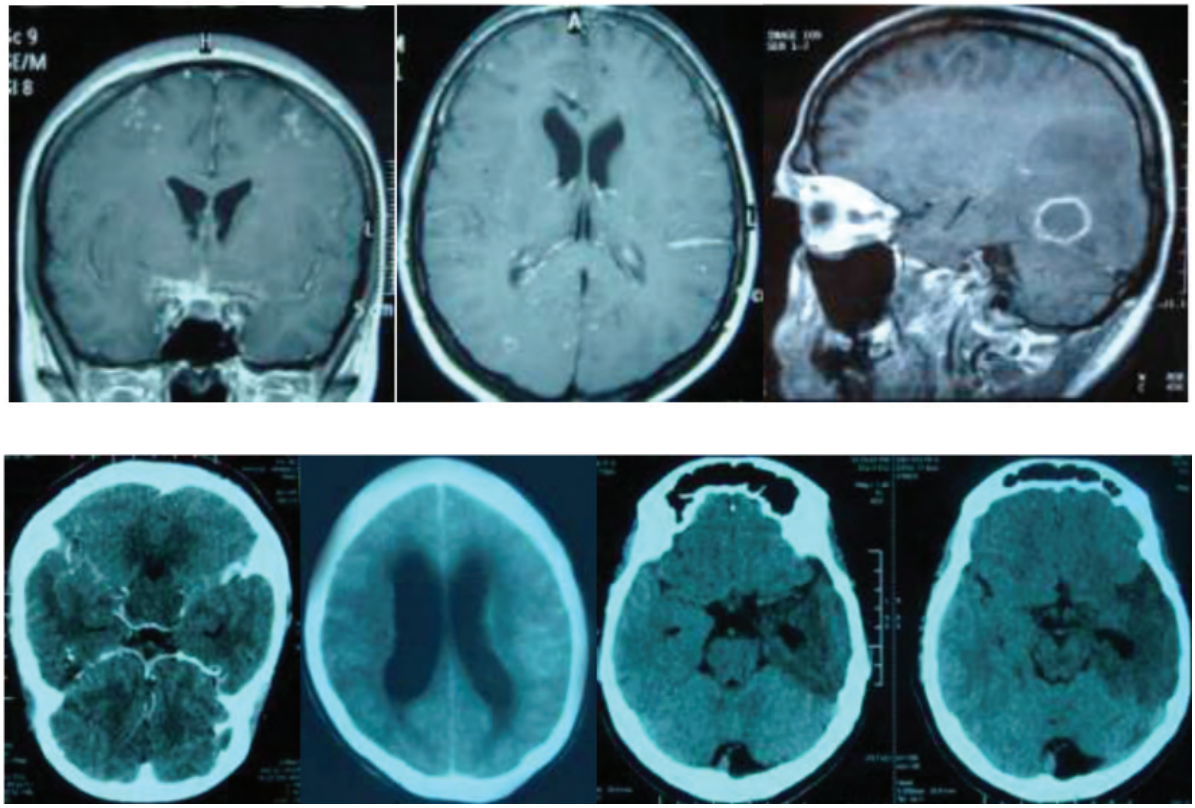

Figure 1. The common neuroradiological findings related with TBM.

a) Coronal T1-weighted contrast enhancement MRI scan shows bilateral multiple millimetric nodular parenchymal lesions (tuberculoma). There is a condensed contrast enhancement that shows basal involvement. b) Axial T1-weighted contrast enhancement MRI scan shows multiple parenchymal nodular lesions. c) Sagittal T1-weighted contrast enhancement MRI scan shows a suboccipital supratentorial ring contrast enhancement lesion with peripheral diffuse edema. This image may be confused with a metastatic mass lesion or pyogenic abscess; however, in this patient, since diagnosis was confirmed by the isolation of *M. tuberculosis* from CSF and the regression was determined in the lesion after specific therapy, metastasis or abscess was excluded by consulting with neurosurgeons. d) T1-weighted axial and coronal MRI contrast enhancement images show infra- and supratentorial bilateral multiple nodular infiltrations. e) Axial CT scans without contrast enhancement show ventricular dilatation and acute hydrocephalus (dilatation in lateral ventricles, transependymal movement of CSF from the ventricular system into the brain parenchyma, and loss of sulcal markings). f) Axial CT scans without contrast enhancement show diffuse cerebral infarction in the left temporal medial region.

Hydrocephalus was detected in 28 (21%) patients: 17 recovered with medical treatment, 11 required neurosurgical intervention, and 2 developed a shunt infection caused by *Acinetobacter baumannii*. The hydrocephalus disappeared within 4 months in 8 of the patients, and 3 patients required a ventriculoperitoneal shunt.

Chest X-rays were obtained from only 101 of the 160 patients due to the inappropriate conditions of some patients. Chest radiography was abnormal in 73 (72%) of the 101 patients. Upon admission, active infiltration (36%), miliary shadowing (25%), sequelae lesions (10%), cavitary lesions (7%), and pleurisy (6%) were the most frequent lesions in 29 patients with normal chest X-rays. In Figure 2, the miliary shadowing and cavitary lesions of 2 patients by X-ray and CT are shown.

Follow-up

There were neurological findings in 110 patients on admission. Standard ATT with 4 drugs began within 1-33 days of hospitalization and lasted for 12-18 months. The median hospitalization time of the

Table 2. Patients with tuberculomas classified according to the TCI.

Tuberculomas	Solitary (n: 16)	Multiple (n: 33)	Total (n: 49)
Size			
<1 cm.	13	25	38
1-2 cm.	3	6	9
≥2 cm	-	2	2
Location			
Cerebellar	3	10	13
Frontal	3	8	11
Temporoparietal	1	6	7
Basal ganglions	4	6	10
Other	5	3	8
Caseating necrosis			
Yes	2	1	3
No	14	32	46

Table 3. Neuroimaging features of 134 TBM cases by CT or MRI.

Findings	n	%
Tubercles	49	36.6
Basal meningitis	36	26.9
Leptomeningeal involvement	34	25.4
Hydrocephalus	28	20.9
Edema	16	11.9
Ischemia-infarct	12	8.9
Abscess	5	3.7
Arachnoiditis	3	2.2
Normal	30	22.4

Table 4. Comparative cranial CT and MRI signs in 27 patients with TBM.

Findings	CT	MRI	Difference
Basal enhancement	3	6	3
Tuberculomas	4	6	2
Leptomeningeal involvement	3	5	2
Hydrocephalus	2	3	1
Infarct	1	3	2
Edema	2	3	1
Abscess	0	1	1
Normal	13	5	8

160 TBM patients was 32 days. During the follow-up period, 27 (17%) patients died and 20 (13%) of the survivors had neurological sequelae at 6 months. The majority of patients died within the first 10 days. Radiological findings of the patients who recovered, died, and had neurological sequelae are summarized in Table 5.

Discussion

TBM is the most common cause of chronic meningitis in developing countries. It affects the industrialized countries by means of global migration of population and the HIV/AIDS epidemic (11,17). In Turkey, tuberculosis is still an endemic public health problem.

The controversial pathogenetic mechanisms of TBM associated with a dense basal meningeal exudate often result from a Rich focus. Basal meningeal enhancement, hydrocephalus, and basal ganglia infarctions form the common triad of neuroradiological findings, and tuberculomas are assessed as the most characteristic lesions of TBM (18). These neuroradiological findings could aid in the diagnosis of TBM. The usage of CT is well established in diagnosing TBM and predicting its complications. Serial evaluations by CT scanning are also useful

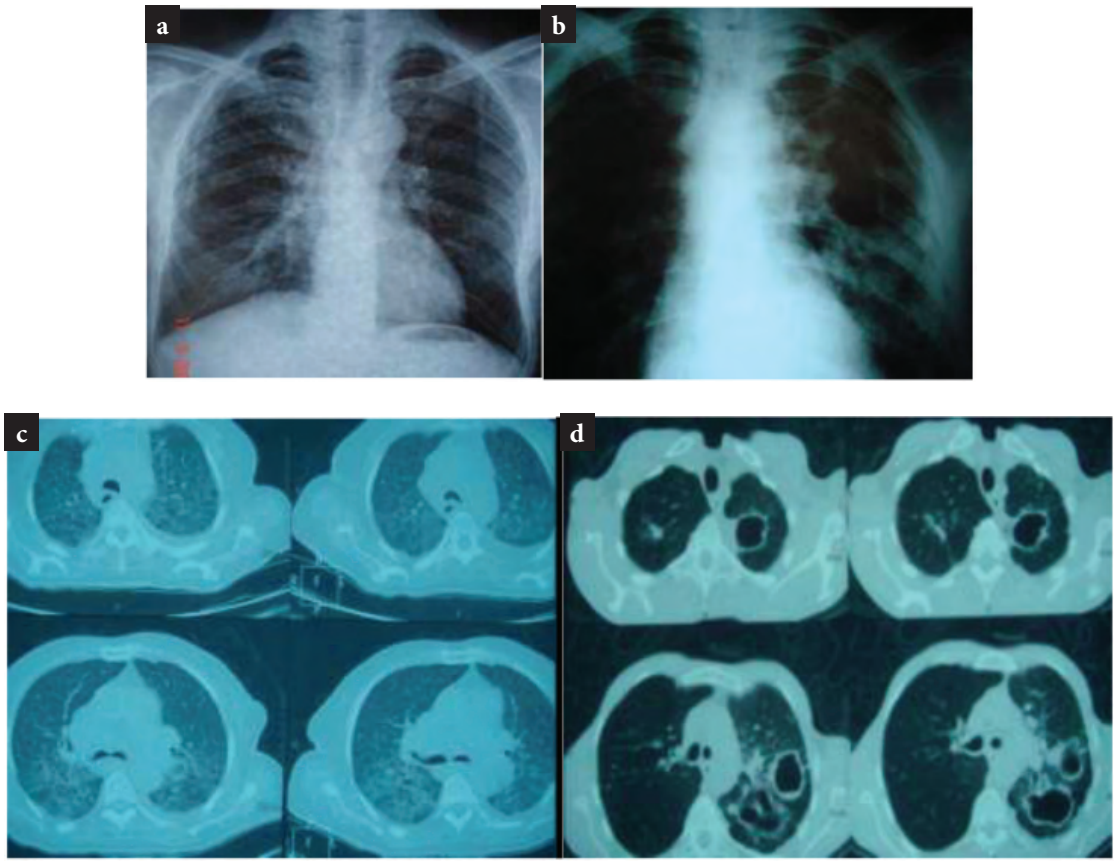

Figure 2. The common radiological findings related with pulmonary TB.

a) Thorax roentgenogram shows miliary pattern (tuberculosis). b) Thorax roentgenogram shows cavitary lesions with peripheral infiltration in left pulmonary lobe. c) Axial thorax CT scans shows diffuse parenchymal miliary shadowing. d) Axial thorax CT scans with contrast enhancement shows cavitary lesions with peripheral infiltration in left lung.

for following the course of hydrocephalus (19,20). Surgical shunting should be considered early on in patients with hydrocephalus diagnosed by follow-up CT and symptoms of raised intracranial pressure. Some studies comparing CT to MRI concentrated on some MRI features of TBM such as tuberculomas and infarcts, and their locations (21,22). A recent study mentioned the more diagnostic and predictive facilities of MRI for poor outcomes compared to CT (18). Indeed, among 27 patients who had both CT and MRI scans, the CT findings were normal in 37% of the patients, while the MRI findings suggested TBM. Basal enhancement, infarct, tuberculomas of <1 cm, leptomeningeal involvement, and edema were different findings that showed up earlier by cranial MRI in contrast to CT. Clearly, MRI is an excellent tool for detecting basal enhancement and infarction in TBM. In addition, specific neuroradiological findings associated with TBM were found in only 61% of the patients that underwent cranial CT, while those same findings were 88% in patients who underwent MRI. Therefore, we suggest that MRI is a more effective and superior imaging technique as compared to CT for diagnosis of TBM, in keeping with previous reports (18,21,22).

The definitive microbiological diagnosis of TBM depends on demonstrating *M. tuberculosis* by smear or culture of the CSF, meninges, or brain tissue. However, this process is time-consuming and has a low yield (1,2,23). The diagnosis of the disease was confirmed by high culture positivity (40%), along with the clinical and CSF findings and neuroimaging signs, in the present study, but the mean growing time of the agent in Lowenstein-Jensen medium

Table 5. Radiological findings of patients who recovered, died, and had neurological sequelae.

Radiological findings	Patients who recovered (n: 113)		Patients with sequelae (n: 20)		Patients who died (n: 27)	
Cranial CT or MRI	**n**	**%**	**n**	**%**	**n**	**%**
Tubercles	36	**23**	8	**40**	5	**19**
Basal meningitis	20	**18**	7	**35**	9	**33**
Leptomeningeal involvement	26	**23**	3	**15**	5	**19**
Hydrocephalus	14	**12**	6	**30**	8	**30**
Edema	12	**11**	3	**15**	1	**4**
Ischemia-infarct	7	**6**	2	**10**	3	**11**
Abscess	3	**3**	2	**10**	0	**0**
Arachnoiditis	2	**2**	0	**0**	1	**4**
Normal	25	**22**	2	**10**	3	**11**
Could not be performed	17	**15**	2	**10**	7	**26**
Chest X-ray						
Active infiltration	23	**20**	3	**15**	10	**38**
Miliary	17	**15**	3	**15**	5	**19**
Sequelae of TB	7	**6**	2	**10**	1	**4**
Cavitary lesion	5	**4**	2	**10**	0	**0**
Pleurisy	6	**5**	0	**0**	0	**0**
Normal	24	**21**	4	**20**	0	**0**
Could not be performed	39	**35**	8	**40**	12	**44**

was 24 days. Therefore, clinicians should use neuroradiological techniques to obtain clues for TBM in addition to patient history and clinical and CSF findings. The innovation of recent imaging facilities such as MRI, and diffusion-weighted or dynamic contrast-enhanced MRI has enhanced clinicians' diagnostic certainty and increased case detection (17,24,25).

Tuberculomas were detected in 49 of the patients in this study (37%). In 42 patients, tuberculomas were detected on admission, and 7 developed tuberculomas during the therapy. Tuberculomas are common forms of CNS TB. They represent 5%-34% of all of the intracranial masses (9,26) and may be confused with other space-occupying lesions. Tuberculomas were evaluated according to their number, size, structure, and location features, and the TCI classification system was developed. It is suggested that this index provides a nominal tuberculoma scale for definition, comparison, follow-up, and differentiation of these intracranial masses in patients with TBM. Tuberculomas are frequently multiple (67%) and located in the frontoparietal region and the basal ganglions (9,27,28). According to the TCI, the location of solitary lesions was infra- or supratentorial, mostly in the basal ganglions and cerebellar hemispheres, while multiple lesions were especially common in the frontal hemispheres and the basal ganglions. In this study, the diameter of the tuberculomas ranged between 3 mm and 4 cm; 96% were smaller than 2 cm, most of them were <1 cm, and these findings were in keeping with similar reports (9,29). During the follow-up period, the radiological response to 12-18 months of ATT was evaluated in ≥90% of patients with tuberculomas. However, in 7 patients, tuberculomas developed within the first 2 months of ATT. Paradoxical reaction during effective ATT is a well-known phenomenon (30-32). The development of new tuberculomas under ATT is thought to have an immunological basis

caused by enhanced host inflammatory response to mycobacterial products (33). Therefore, using systemic corticosteroids in patients thought to have a paradoxical reaction suppressed this immunological response in our study, like in previous reports (30,34).

Hydrocephalus is a common complication of TBM, and its reported frequency varies from 12% to 77% in patients with TBM and from 12% to 32% in adult TBM patients in most series (1,8,20,22,24,33,35). This differentiation arises from the features of study groups. Hydrocephalus is reported to be much higher in children than in adult TBM series (18,20). Therefore, our findings are similar to these reports (21%). Of the patients with hydrocephalus, 8 died, and 2 who only had CT scans were also found to have basal meningitis. The other 6 deceased patients with hydrocephalus who had MRI scans had tuberculomas (in 2 patients), basal meningitis (in 4), infarct (in 1), and leptomeningeal involvement (in 2) in their cranial imaging. Enlarged ventricles, which were considered for neurosurgical drainage (39%), were found in 11 of the 28 patients with hydrocephalus, and 2 had a shunt infection caused by *Acinetobacter baumannii*. The hydrocephalus disappeared within 4 months in 8 of the patients, and 3 required a ventriculoperitoneal shunt.

Basal exudate was detected in 27%, diffuse or focal meningeal enhancement in 25%, and ischemia/infarcts in 9% of the patients. The cerebral infarction in TBM was reported as a major cause of long-term morbidity in some studies (12,24). The predominant basal exudates causing periarteritis may result in obliterative vasculitis and infarction. Previous studies reported the incidence of infarction in TBM as ranging from 13% to 53% (12). In this study, there were 12 patients with ischemia/infarcts, and 8 of them had basal meningitis or leptomeningeal involvement. The median age of these patients was 55 years, and 9 patients were in advanced stages. During the follow-up period, 3 patients died and 2 had neurological sequelae. Eventually, in these patients, vasculitic lesions were assessed as newly determined infarcts, which were associated with TBM by our consultant neurologists.

Active pulmonary TB was detected in 29% of the patients and 27% had a previous history of TB. The frequency of chest X-ray findings was different in those patients who survived compared to those who died. Active infiltration and miliary shadowing were more common in those who died than in the survivors. The presence of active pulmonary TB was significantly higher in the patients who died ($P = 0.019$).

The data having been obtained retrospectively from the patients' hospital files was the probable limitation of this study. The results were based on data collected retrospectively in an uncontrolled manner. Some other diagnostic and radiological procedures might have been performed if a prospective study had been designated previously.

The presence of extrameningeal TB, and especially pulmonary involvement and neuroradiological findings such as tuberculoma, basal meningitis, or hydrocephalus, are helpful for the diagnosis of TBM in the early stages in which microbiological results could not be obtained. MRI and CT scanning are also critical in predicting the outcome and in evaluating the complications of the disease that require neurosurgical intervention. Moreover, MRI may provide specific findings associated with TBM, and, if available, it should be performed for all patients in the early stage of the disease to detect specific signs related with poor outcome. The TCI may be useful as a standard nominal scale for differentiating, following, and comparing tuberculomas as differentiated from the other space-occupying lesions.

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