Evaluation of 121 adult cases of tuberculous meningitis

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ABSTRACT

الأهداف: لتقييم الأعراض الخطيرة لمرض التهاب السحايا التدرني (TBM)، والناتج عن صعوبة تشخيص وعلاج هذا المرض.

الطريقة: تم تقييم النتائج المخبرية والسريرية لـ 121 مريضاً مصاباً بالتهاب السحايا التدرني (TBM) والتي تمت متابعتهم في الفترة ما بين عام 1998م وحتى عام 2005م على التوالي. تم تشخيص حالة المرضى بواسطة التاريخ المرضي، نتائج الفحص الطبي، نتائج فحص السائل النخاعي الشوكي (CSF)، مزرعة السائل النخاعي الشوكي، والتقنيات التصويرية. تمت معالجتهم بعقار آسونيازيد، وريفامبيسين، وإثامبوتول، وبرازيناميد، وديكساميثازون.

النتائج: كان توزيع العمر للمرضى البالغ عددهم 121 مريضا 15-70 (31±14.0) عاماً، وكان الصداع هو أكثر المشاكل تكراراً عند الدخول، وكان التصلب الفقري والتغير في الوعي والحمى أكثر النتائج تكراراً. أربعة وأربعون مريضاً مصاباً بالدرن الرئوي النشط، 33 منهم مصاباً بالدرن الرئوي، و24 لديهم فرد من العائلة يعاني من الدرن الرئوي النشط، ولدى مريض واحد إصابة بفيروس نقص المناعة (الإيدز). تم عزل بكتريا الدرن من السائل النخاعي الشوكي (CSF) في 52 مريض (43%). كانت أكثر النتائج شيوعاً عند التصوير القحفي هي: التهاب السحايا القاعدي، والتورم الدرني، واستسقاء الرأس. تلقى المرضى البالغ عددهم 121 العلاج وشفي منهم 69 مريضاً بالكامل، بينما شفي 40 مريضاً مع الإصابة بمشاكل عصبية، وتوفي 12 مريضاً. كان 10 مرضى من المتوفين مصاباً بالتهاب السحايا التدرني من الدرجة الثالثة (III TBM).

خاتمة: يعتبر التهاب السحايا التدرني (TBM) من أحد أكثر الأشكال السريرية شدة للدرن، ويرتبط معدل الوفيات بشكل مباشر مع مرحلة المرض.

Objectives: To evaluate serious complications of tuberculous meningitis (TBM), resulting from difficulties in diagnosis and treatment of the disease.

Methods: Clinical and laboratory findings of 121 patients with TBM followed-up between the years 1998 and 2005 were evaluated retrospectively in Haseki Training and Research Hospital, Istanbul, Turkey. The patients were diagnosed by history, physical examination findings, CSF findings, CSF culture, and radiological imaging techniques, and were treated with isoniazid, rifampicin, ethambutol, pyrazinamide, and dexamethasone.

Results: The age distribution of 121 patients was 15-70 (31±14.0 years). Most frequent complaint on admission was headache, and most frequent findings were nuchal rigidity, alteration in consciousness, and fever. Forty-four patients had active pulmonary tuberculosis, 33 had a history of pulmonary tuberculosis, 24 had a family member with active pulmonary tuberculosis, and one had HIV infection. *Mycobacterium tuberculosis* was isolated from CSF in 52 patients (43%). At cranial imaging, basal meningitis, tuberculoma, and hydrocephalus were the most common findings. Of 121 patients who were treated, 69 recovered completely, 40 recovered with neurological sequels, and 12 patients died. Ten of the deceased had stage III TBM.

Conclusion: Tuberculous meningitis is one of the most severe clinical forms of tuberculosis. Mortality is directly related with the stage of the disease.

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Tuberculosis (TB) caused epidemics, reaching a peak in the crowded cities in the 18th century due to poor sanitary conditions. In the second half of the 20th century, discovery of antituberculous drugs stopped the rise of TB, although currently acquired immunodeficiency syndrome (AIDS) has increased the number of patients with TB again, and there is a parallel increase in tubercular meningitis (TBM). The first reported TBM in the literature before Robert Koch's discovery of *Mycobacterium tuberculosis (M. tuberculosis)*, was reported in Lancet in 1836,[2] in 6 children who were dying from acute hydrocephalus, in whom tuberculous

meningeal inflammation was detected at post-mortem examination. These cases were designated as TBM.[1,2] Tuberculous meningitis is usually seen in 5-10% of adult patients with TB, and may occur without other organ involvement, or exist coincidentally with pulmonary or miliary infection. Hydrocephalus and adhesive vasculitis leading to cranial nerve involvement, are the main pathological lesions in TBM.[3] Although its cause is known, and there is a vaccine and specific therapy, TBM is still an 'unknown' with multiple facets, causing diagnostic problems, and sequels. Empirical treatment should be started when clinical and CSF findings suggestive of TBM (non-acute clinical presentation, lymphocytic pleocytosis, increase in protein content, and decrease in glucose in the CSF, presence of another TB focus and neuroradiological findings) are present.[3,4] Pulmonary TB cases were treated at the pulmonary medicine clinics, and the patients with extrapulmonary TB were treated and followed up at various clinics in Turkey. Our clinic is a tertiary referral center where a large number of cases of extrapulmonary TB (346 TBM cases in 20 years), especially TBM were treated and followed-up by specialists (infectious disease specialists, neurologists, neurosurgeons, ophthalmologists) with multidisciplinary approaches. All patients presenting with signs and symptoms, suggesting an infection of CNS (signs of meningeal irritation and alteration in consciousness) were hospitalized. The primary goal of the study is to share the data of 121 TBM patients followed in one center, to point out the difficulties in diagnosis and treatment of the disease in the light of literature, to emphasize our local epidemiological characteristics. Besides we wanted to attract attention that Thwaites Diagnostic Index is quite practical and useful for diagnosis of TBM.

Methods. One hundred and twenty-one patients with TBM, diagnosed, treated, and followed-up at our clinic between January 1998-July 2005 were evaluated retrospectively in Haseki Training and Research Hospital, Istanbul, Turkey. Between 1998-2005 all the consecutive patients diagnosed as TBM were included in the study. The epidemiological, clinical, and laboratory features were recorded. Out of the 121 cases, 12 underwent lumbar punctures in the first hour upon admission to the hospital due to unfavorable fundoscopic examination or poor general medical condition and their CSF specimens were inoculated in Lowenstein-Jensen (L-J) culture media for *M. tuberculosis* isolation. Cranial CT or MRI was carried out in 106 patients.

Diagnosis. Tuberculous meningitis' diagnosis in these patients who presented with a clinical picture of lymphocytic meningitis were investigated by history (active pulmonary or extrapulmonary TB on admission, close contact with a person with active pulmonary TB), physical examination, CSF findings (positive CSF culture for *M. tuberculosis*, positive microscopy for acid-fast bacilli from CSF or other body fluids or tissues), and imaging techniques (characteristic radiological findings for TBM on cranial CT or MRI such as exudates in basal cisterns, tuberculoma, hydrocephalus). The clinical response to antituberculous therapy was assessed. The patients were also evaluated with Thwaites' diagnostic scoring, retrospectively for the period between 1998 and 2002, and then prospectively thereafter. The patients with a score of ≤4 were considered as having TBM (**Table 1**).[5]

Clinical stage. The patients were evaluated according to Gordon and Parsons criteria,[6] and classified as stage I, II, or III. Patients with no clouding of consciousness, non-specific findings, and no neurological symptom were considered stage I, while signs of meningeal irritation, lethargy, or alteration in behavior, and minor neurological deficits (cranial nerve palsies) were considered stage II, and severe neurological deficits (paresis), convulsions, abnormal movements, stupor and coma were considered stage III.

Treatment. Combinations of isoniazid (INH), rifampicin (RIF), ethambutol (EMB), streptomycin (SM), pyrazinamide (PZA), and dexamethasone (DXM) according to the neurological evaluation were used in the treatment. The duration of treatment was 9-12 months. In the first 2 months, 4 drugs, 3 of which were PZA, INH, and RIF were used, after which treatment was continued with 2 drugs (INH and

Table 1 - Thwaites' diagnostic index.

Criteria	Diagnostic index
Age (years)	
≥36	2
<36	0
Blood WCC (10^3/mL)	
≥15000	4
<15000	0
History of illness (days)	
≥6	-5
<6	0
CSF total WCC (10^3/mL)	
≥900	3
<900	0
CSF neutrophils (%)	
≥75	4
<75	0

WCC - white cell count, CSF - cerebrospinal fluid

RIF). Other antituberculous medications were used in some patients, according to their antituberculous drug sensitivity profiles. Patients in stage II or III with neurological deficits were treated with 16 mg/day DXM for 8 weeks. All patients stayed at least 4-8 weeks in the hospital while some of them stayed longer according to their general conditions.

Results. Fifty-nine patients (49%) were female, and 62 (51%) were male (range 15-70, mean 31±14). Two-thirds were between 15-30 years of age. Two were pregnant, and one had given birth 4 months earlier. Only one patient had human immunodeficiency virus (HIV) infection. Three hundred and forty-six cases seen in the last 20 years were evaluated to investigate the seasonal pattern of TBM. The mean number of cases in the months of April, May, June, July, and August are above the annual mean value (**Figure 1**).[7] All patients had a score of 4 or less, and the majority (70%) had a score of -5 according to Thwaites' diagnostic scoring. According to Gordon and Parsons Criteria,[6] 15 of the patients (12%) were at stage I, 78 (64%) at stage II, and 28 patients (23%) at stage III. The time from the initiation of symptoms was less than a week in 22 patients (18%), between 1-4 weeks in 75 (62%), and more than a month in 24 patients (20%). Main complaints, findings, and CSF findings of all patients, and the distribution of neurological findings of the 52 patients (that had neurological findings) are presented in **Table 2**. Blood leukocyte count was between 1500-32800 cells/mm^3 (normal value: 4000-10000 cells/mm^3), and they were in the normal range in 86 patients (71%). The mean erythrocyte sedimentation rate was 35 mm/hour, and 25 patients were in the normal range. Among 109 patients in whom a CSF sample was obtained, 109 patients had pleocytosis (100%) (normal value ≤5/mm^3), 100 patients (92%) had decreased glucose levels (normal value: ≥60% of that in blood), 91 patients (83%) had increased protein levels (normal value ≤40mg/dL), and there was a predominance of lymphocytes in 72 patients (66%). *Mycobacterium tuberculosis* was isolated by L-J culture media in CSF samples of 52 patients (48%) (**Table 2**). Pulmonary TB was detected in 44 of 75 patients (59%) by chest x-ray screening upon admission. Other extrapulmonary forms of the disease were observed in 14 patients (5 had Pott's disease, 4 had pleural TB, 2 had peritoneal TB, 2 renal TB, and one patient had tuberculous arthritis). Patients with a previous history of TB were 33 (27%) and 24 had a family history of TB. In 106 (88%) patients, cranial imaging was carried out, and of these, 23 (22%) had no pathological findings. The pathological findings in pulmonary x–ray examination, and the neuroradiological findings of 83 patients were detected in one or more radiological pathologic changes (**Table 3**). Diabetes mellitus (DM), pregnancy, idiopathic thrombocytopenic purpura (ITP), alcoholism, HIV/acquired immune deficiency syndrome (AIDS), and trauma were detected as underlying comorbidities in 17 patients (14%). Standard antituberculous treatment with 4 drugs such as INH, RIF, PZA, and EMB was used in 104 (86%) of the patients for 9-12 months. Patients with neurological deficits, at stage II or III, were given DXM at a dose of 16 mg/day for 8 weeks, at the end of which, the dose of steroid was gradually decreased. Four patients had multi-drug-resistant TB, diagnosed in other hospitals before occurrence of TBM, mostly by cultures of sputum. These patients and other 13 with drug sensitivity findings were treated with suitable antituberculous medications, according to their antituberculous drug sensitivity profiles (INH-RIF-PZA-SM were used in 4, INH-RIF-EMB-PZA-SM in 9, and minor antituberculous drugs in 4). Sixty-nine of the patients (57%) recovered completely, while 33 (27%) recovered with mild neurological sequels (epilepsy, hemiparesis, disturbances of hearing and vision), and 7 (6%) with severe neurological sequels (hemiplegia, debilitation, and so forth). The patient with HIV infection recovered without neurological sequels. In spite of the therapy, 12 patients died (10%), 2 of which were at stage II and 10 at stage III (**Table 4**).

Table 2 - Complaints, findings, neurological signs, and CSF findings at the time of admission.

Complaints, findings, neurological signs and CSF findings	No. of patients (%)
Headache	100 (83)
Nausea - vomiting	77 (64)
Alterations in consciousness	66 (55)
Fever (>38.3°C)	58 (48)
Weight loss	23 (19)
Nocturnal sweating	21 (17)
Diplopia	17 (14)
Cough and sputum	14 (12)
Nuchal rigidity	89 (74)
Alterations in consciousness	66 (55)
Fever	58 (48)
Meningeal irritation signs	49 (41)
Paresis/plegia	17 (14)
Diplopia	17 (14)
Convulsions	11 (9)
Disability in walking	10 (8)
Cranial nerve involvement	8 (7)
Dysarthria	5 (4)
Cell count in CSF (/µl) mean±SD (range)	223.7 ± 268.0 (1-2190)
CSF protein level (mg/dl) mean±SD (range)	162.9 ± 152.1 (10-792)
CSF glucose level (mg/dl) mean±SD (range)	38.4 ± 21.8 (5-127)
Positivity of culture in CSF	52 (43)

CSF - cerebrospinal fluid

Table 3 - Radiological and neurological findings.

Findings	N (%)
Chest x-ray	
Miliary	18 (24)
Active infiltration	15 (20)
Cavitary lesion	7 (9)
Sequels of TB	6 (8)
Pleurisy	4 (5)
Normal	31 (41)
Neurological (cranial CT or MRI)	
Tubercles	34 (32)
Basal meningitis	39 (37)
Hydrocephalus	18 (17)
Ischemia -infarct	6 (5)
Arachnoiditis	2 (2)
Abscess	2 (2)
Edema	2 (2)
Normal	23 (22)

Table 4 - Outcomes according to stages.

Outcomes	Stage I	Stage II	Stage III	Total
Recovery	9	41	7	57
Mild neurological sequels	3	19	5	27
Severe neurological sequels	0	2	3	6
Death	-	2	8	10
Total	**12**	**64**	**23**	**100**

Data are expressed as percentage

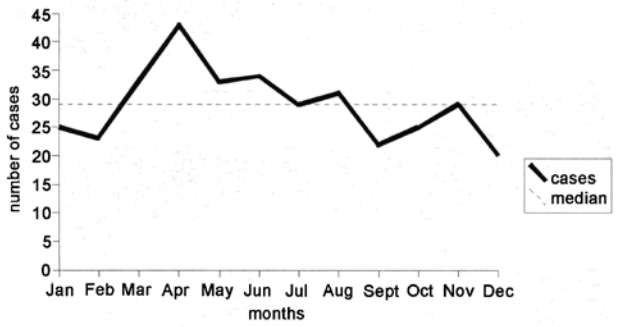

Figure 1 - Seasonal distribution of tuberculosis meningitis patients in 20 years.

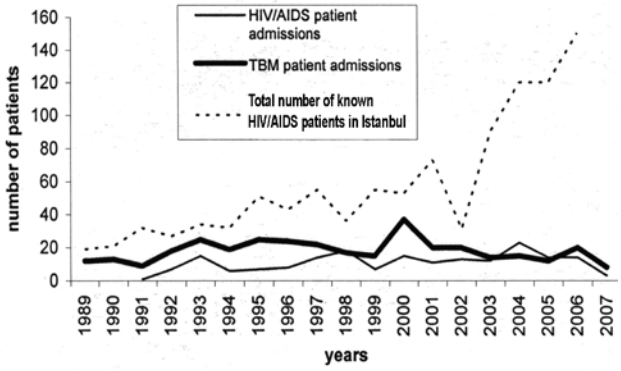

Figure 2 - Distribution of tuberculous meningitis and HIV/AIDS patients between 1989 and 2007.

Six of the patients, who died, had an underlying disease (alcoholism, cirrhosis, ITP, DM, trauma, and DM plus trauma).

Discussion. Experience has shown that, no one can ascertain when a person will contract TB disease and will have TBM. Tuberculous meningitis is an insidious illness, and most patients seek medical care only if the disease is in the advanced stages, the outcome is poor, with severe sequels, and high mortality, although the cause and pathophysiology of TB are known for more than a century, and there are both a vaccine and a specific treatment for this illness. Prevention of TBM is possible only by prevention and control of TB. The incidence of TB has been reported as 25/100000 in the general population in Turkey. However, this rate is 48/100000 in Istanbul, which is relatively high, like in other metropolis.[8] Also, the number of HIV/AIDS patients is higher than the other regions of Turkey (a total of 2500 reported cases in Turkey since 1985, and 1087 [nearly half of the cases] from Istanbul). Tuberculosis and HIV/AIDS are more frequently seen together worldwide in recent years, although the number of HIV/AIDS patients was only 150 in Istanbul in 2006 (**Figure 2**).[9] As a result of this low prevalence, the contribution of HIV/AIDS is not prominent in our group of patients with TBM. We detected HIV/AIDS in only one patient. The trend in the last 20 years in our hospital (which is an important tertiary referral center for both TBM and HIV/AIDS) shows a modest increase in the number of HIV/AIDS. However, there is no parallel increase in patients with TBM, which suggest that HIV/AIDS does not contribute to TBM incidence in Istanbul (**Figure 2**).[9]

In 58 of our patients, different clinical forms of TB were detected with TBM (pulmonary TB, Pott's disease, and pleural, peritoneal, renal, synovial TB). Tuberculosis history was reported in 33 cases (27%), and there was active pulmonary TB history in the family in 24 patients (20%). In several series regarding TBM patients living in other regions of Turkey, active TB or TB history was detected in 7-87% cases. The rate of TB history in the family or close contact with person with active pulmonary TB is low in adult TBM

patients in developed countries. However, in developing countries such as Turkey, patients with TBM have poor socioeconomic conditions, it is not surprising for the high rate of positive family histories.[10] Tuberculous meningitis is generally a meningitis form with subacute clinical course, however, acute presentation may also be seen.[11] The time from the initiation of symptoms was <1 week in 22 patients (18%), and 1-4 weeks in 75 (62%). Most of TBM patients admitted in the hospital were in stage II case. In the absence of signs of another TB form or TB history, the non-specific findings in stage I may be easily missed in most healthcare facilities. Two thirds (64%) of our patients were in stage II, and 23% were in stage III upon admission, whereas in a study by Hosoğlu et al,[12] 36% of the cases were in stage II, and 28% in stage III in other regions of Turkey. In other studies from Turkey, most of the patients were in stage II upon admission.[4,11,13-15] Fifty-two of our cases (43%) had focal or generalized neurological deficits on admission. The most frequently detected neurological findings were paresis/plegia, diplopia, and convulsions. In some studies,[4,16] this rate was low. However, Avci et al[15] reported that all TBM patients (except one) had neurological deficits upon hospital admission. Obviously, delay in diagnosis and treatment due to insidious course of TBM, may cause progression of the neurological deficits. The severity of the neurological signs upon admission is directly correlated with neurological sequels and mortality, and is an important factor in prognosis.[17-19] In the present study, the rate of neurological sequels was 33% in patients with complete recovery, while 10 of the patients who died were in stage III. The patients were decided to observe long term follow up of the neuroradiological lesions and the effect to the TBM recurrence.

Definitive diagnosis of TBM is made by detecting or isolating the organism in CSF, although this may not be possible in every patient. It is possible to show acid fast bacilli in CSF specimens by Ziehl-Neelsen stain in 10-40% of the patients, and CSF cultures are positive in 5-90% of cases, frequently in less than half.[4,13,16,20,21] In the current study, *M. tuberculosis* was isolated in the CSF of patients (43%). Thwaites et al[5] developed a scoring system for early diagnosis of TBM. Such a measure may be helpful in the period when symptoms of TBM are subtle, and non-specific. All our patients had a score of ≤4, which strengthens the diagnosis of TBM, and 70% of the patients had a score of -5. Of 106 patients in whom a cranial CT/MRI study was performed, 83 patients had one or more radiological finding. In some series, it is shown that basal meningitis, hydrocephalus, tuberculoma, and infarct are the most frequent findings in cranial imaging in patients with TBM, and basal meningitis and tuberculoma's coexistence are specific for TBM.[12,17,22] Since it is suggested in recent years that diagnosis and follow-up of TBM should be carried out with MRI,[23] cranial MRI was preferred to CT in the second half of this study. Obviously, a delay in diagnosis and treatment will cause an increase in the neurological damage, and a comorbidity may also have an adverse impact on prognosis.[17,18] In the present study, 10 of the patients who died were in stage III, and half had comorbidities. These 2 features emerge as the most important prognostic factors.

In conclusion, TBM is a serious disease causing severe neurological damages and mortality. Tuberculous meningitis occupies an important place in the differential diagnosis of cases with headache, nausea, vomiting, nuchal rigidity, and alterations in consciousness. Keeping this fact in mind will provide early diagnosis and treatment, and will decrease both the rate of neurological sequels and deaths due to TBM.

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References

1. Thwaites GE, Tran TH. Tuberculous meningitis: many questions, too few answers. ***Lancet Neurol*** 2005; 4: 160-170.
2. Koch R. Die Atiologic der Tuberkulose. ***Berliner Klinische Wochenschrift*** 1882; 15: 221-230.
3. Dastur DK, Manghani DK, Udani PM. Pathology and pathogenetic mechanisms in neurotuberculosis. ***Radiol Clin North Am*** 1995; 33: 733-752.
4. Goktas P, Ceran N, Coskun D, Hitit G, Karagul E, Ozyurek S. Evaluation of 38 adult cases of tuberculous meningitis. ***Klimik Derg*** 1998; 11: 15-18.
5. Thwaites GE, Chau TT, Stepniewska K, Phu NH, Chuong LV, Sinh DX, et al. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. ***Lancet*** 2002; 360: 1287-1292.
6. Gordon A, Parsons M. The place of corticosteroids in the management of tuberculous meningitis. ***Br J Hosp Med*** 1972; 7: 651-655.
7. Sengoz G, Nazlican O. An assessment of the TB meningitis cases handled in our clinic between the years 1989-1993. ***Haseki Medical Bulletin*** 1994; 32: 67-70.
8. Statistics: Basic Health Services Annual 2006. (December 2007). Available from URL: http://www.saglik.gov.tr
9. Provincial Health Directorate of Istanbul Statistics; 2006. (December 2007). Available from URL: http://www.istanbulsaglik.gov.tr/w/sb/bh/aidsbulasici.asp
10. Arinc S, Arinc B, Yaldız E, Agca M, Aktas O, Durucu M, et al. Evaluation the socioeconomic features of patients with tuberculosis. ***Klimik Derg*** 2002; 15: 82-84.
11. Tasova Y, Saltoglu N, Yaman A, Aslan A, Dundar IH. Evaluation of 17 cases of adult tuberculous meningitis. ***Flora*** 1997; 2: 55-60.

12. Hosoglu S, Geyik MF, Balik I, Aygen B, Erol S, Aygencel SG, et al. Tuberculous meningitis in adults in Turkey: epidemiology, diagnosis, clinic and laboratory. ***Eur J Epidemiol*** 2003; 18: 337-343.
13. Yuce P, Celik I, Kalkan A, Demirdag K, Cihangiroglu M. Tuberculous meningitis: Report of thirty cases. ***Flora*** 2003; 8: 226-231.
14. Yaramis A, Gurkan F, Elevli M, Soker M, Haspolat K, Kirbas G et al. Central nervous system tuberculosis in children: a review of 214 cases. ***Pediatrics*** 1998; 102: 49-53.
15. Avci M, Ozgenc O, Ari A, Mermut G, Coskuner A, Kururuzum Z, et al. The evaluation of cases of tuberculous meningitis. ***Turkish J Infect*** 2007; 21: 117-122.
16. Kent SJ, Crowe SM, Yung A, Lucas CR, Mijch AM. Tuberculous meningitis: a 30-year review. ***Clin Infect Dis*** 1993; 17: 987-994.
17. Cagatay AA, Ozsut H, Gulec L, Kucukoglu S, Berk H, Ince N, et al. Tuberculous meningitis in adults-experience from Turkey. ***Int J Clin Pract*** 2004; 58: 469-473.
18. Hosoglu S, Geyik MF, Balik I, Aygen B, Erol S, Aygencel SG, et al. Predictors of outcome inpatients with tuberculous meningitis. ***Int J Tuberc Lung Dis*** 2002; 6: 64-70.
19. Misra UK, Kalita R, Roy AK, Mandal SK, Srivastava M. Role of clinical, radiological, and neuropsychological changes in predicting the outcome of tuberculous meningitis: a multivariable analysis. ***J Neurol Neurosurg Psychiatry*** 2000; 68: 300-303.
20. Ulusoy S, Ozer O, Tasdemir I, Buke M, Yuce K, Serter D. Tuberculous meningitis: Evaluating of forty-three cases according to clinical, laboratory features, treatment and prognosis. ***Infeks Derg*** 1995; 9: 375-378.
21. Qureshi HU, Merwat SN, Nawaz SA, Rana AA, Malik A, Mahmud MK, et al. Predictors of inpatient mortality in 190 adult patients with tuberculous meningitis. ***J Pak Med Assoc*** 2002; 52: 159-163.
22. Sunbul M, Atilla A, Esen S, Eroglu C, Leblebicioglu H. Thwaites' diagnostic scoring and the prediction of tuberculous meningitis. ***Med Princ Pract*** 2003; 14: 151-154
23. Kilani B, Ammari L, Tiouiri H, Goubontini A, Kanoun F, Zouiten F. Neuroradiologic manifestations of central nervous system tuberculosis in 122 adults. ***Rev Med Interne*** 2003; 24: 86-96.

REFERENCES

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