Prognostic factors of neurological sequel in adult patients with tuberculous meningitis

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ABSTRACT

الأهداف: تقييم مؤشرات العواقب العصبية التي يعاني منها مرضى التهاب السحايا السُلي.

الطريقة: تم إجراء هذه الدراسة الاسترجاعية في قسم الأمراض المعدية والميكروبولوجيا بمركز هاسيكي للأبحاث والتدريب، اسطنبول، تركيا وذلك خلال الفترة من يناير 1998م إلى مارس 2009م. شملت الدراسة 160 مُصاباً بمرض التهاب السحايا السُلي حيث تم تحليل العواقب العصبية المترتبة على هذا المرض خلال 6 أشهر. ولقد تم استخدام تحليل الانحدار اللوجستي متعدد المتغيرات (multivariate logistic regression) من أجل دراسة توقعات سير المرض الخاصة بالنتائج السريرية، والديموغرافية، والإشعاعية، والمعملية وقت دخول المستشفى، بالإضافة إلى تطور العواقب العصبية، فيما تم تحديد النتائج السريرية والعلاجية خلال 6 أشهر باستخدام النسخة المُعدلة من مؤشر بارثيل (Barthel Index).

النتائج: أظهرت النتائج بأن 27 مريضاً (17%) قد توفوا، فيما أُصيب 20 (13%) مريضاً ببعض العواقب العصبية وذلك خلال 6 أشهر. أشارت النتائج بأن شلل العصب القحفي، والورم السُلي، وصغر السن، والتهاب السحايا القاعدي من أكثر الأعراض العصبية التي تدل على وجود العواقب العصبية وذلك اعتماداً على التحليل أحادي المتغيرات. وأشار تحليل الانحدار اللوجستي متعدد المتغيرات بأن كلاً من صغر السن (OR 2.9, 95% CI 1.0–8.6, p=0.049)، وشلل العصب القحفي (OR 3.9, 95% CI 1.8–8.8, p=0.001)، والورم السُلي (OR 1.9, 95% CI 1.0–4.2, p=0.048) من أكثر الأعراض العصبية التي تشير إلى وجود هذه العواقب العصبية.

خاتمة: أظهرت هذه الدراسة بأن العواقب العصبية تكون شائعة كثيراً في المرضى المصابين بالورم السُلي، وشلل العصب القحفي أثناء دخول المستشفى، وأن المشاكل العصبية قد تحدث بالرغم من التدخل العلاجي السريع والفعال و خصوصاً مع المرضى الصغار في السن.

Objectives: To evaluate the predictors of neurological sequel in tuberculous meningitis (TBM).

Methods: This study was carried out at the Department of Clinical Microbiology and Infectious Diseases, Haseki Training and Research Hospital, Istanbul, Turkey, between January 1998 and March 2009. Neurological sequels at 6 months of 160 adult patients with TBM who had been followed up were assessed retrospectively. The prognostic role of various demographic, clinical, laboratory, and radiological findings on admission, in prediction of neurological sequel development, were studied using a multivariate logistic regression. Clinical and therapeutic outcomes at 6 months were determined using a modified Barthel Index.

Results: Twenty-seven (17%) patients died and 20 (13%) survivors had neurological sequelae at 6 months. Cranial nerve palsy, presence of tuberculoma, younger age, and basal meningitis were found to be significant predictors of neurological sequelae in univariate analysis, but only younger age (odds ratio [OR] 2.9, 95% confidence intervals [CI] 1.0-8.6, *p*=0.049), cranial nerve palsy (OR 3.9, 95% CI 1.8-8.8, *p*=0.001), and presence of tuberculoma (OR 1.9, 95% CI 1.0-4.2, *p*=0.048) were found to be significant predictors using multivariable logistic regression analysis.

Conclusion: Neurological sequelae were more common in patients with tuberculoma and cranial nerve palsy on admission. Development of neurological complications may be seen despite timely and effective anti-tuberculous therapy especially in younger patients.

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Tuberculosis (TB), continues to be a major global health problem worldwide. The World Health Organization (WHO) reported 9.27 million new cases of TB and 1.3 million TB-related deaths among an HIV negative population in 2007.[1] Tuberculous meningitis (TBM) is the most common form of CNS TB, and is still a serious cause of morbidity and mortality in developing countries. Prediction of TBM outcome is difficult due to its protracked course, virulence of the agent, underlying pathological mechanisms, and variation of host immunity.[2] Advanced stage and neurological findings on admission or neuroradiological signs were determined previously as predictors of death and neurological sequelae of TBM.[2-7] There are few reports on neurological sequel predictors in patients with TBM in the literature. The purpose of the present study is to describe the neurological findings of 160 patients with TBM who had been followed up for 11 years, and to determine the predictors for neurological sequelae within 6 months after diagnosis of TBM.

Methods. *Patient population and setting.* Istanbul, Turkey has a high rate of TB and a large proportion of patients with extrapulmonary TB, especially TBM, receive care in the Haseki Training and Research Hospital, Istanbul, Turkey, which is a 550-bed tertiary referral center hospital providing primary and tertiary care in the Istanbul metropolis and the northwest region of Turkey. All patients' ≥15 years old, who were diagnosed with TBM in our hospital between January 1998 and March 2009 were included in this study. Seven patients were excluded due to incomplete data. Data were collected using a standard data collection form. The clinical course and a 6-month outcome of patients data were obtained from patients' hospital files, discharge summaries, and outpatient records retrospectively. According to the current local regulations, the institutional review board or ethics committee approval for the research protocol for retrospective studies is not required.

The diagnosis of TBM was based on clinical, CSF, and neuroimaging signs. In this study, the patients with lymphocytic meningitis (fever and headache with nuchal rigidity or altered sensorium for more than 2 weeks, pleocytosis, protein increase and glucose decrease in CSF) were considered as TBM in addition to at least one of the following criteria: 1) a positive culture or positive microscopy for acid-fast bacilli (AFB) or polymerase chain reaction (PCR) of CSF, body fluids, or tissues for *Mycobacterium tuberculosis* (MTB); 2) close contact with a person with active pulmonary TB; 3) radiological findings on cranial CT/MRI (characteristic of TB such as exudates in basal cisterns, hydrocephalus or tuberculoma) or chest x-ray; 4) clinical response to antituberculous therapy. 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.[8]

The clinical stage of patients was assessed according to the British Medical Research Council (MRC) criteria: stage I - patients with no neurological findings, stage II - patients with focal neurological signs, and stage III - patients with severe neurological findings or coma.[9] Functional outcome was defined on the basis of 6-month Barthel Index (BI) score: poor (BI <12), partial (BI= 12-20), and complete (BI=20) recovery.[10]

Evaluation. Neurological sequelae at 6-months of the 160 patients with TBM who had been followed up for 11 years in a tertiary referral center hospital were assessed retrospectively. Neurological features associated with TBM were obtained with an elaborative neurological examination, both on admission and at 6-months. Consciousness statement, presence of cranial nerve palsy (CNP), paresi, or plegia according to muscle power, tone, and reflexes, presence of visual impairment, gait abnormality, and convulsion were noted. Neuroimaging signs such as basal meningeal enhancement, hydrocephalus, basal ganglia infarctions, and tuberculoma (multiple or solitary; usually ≤2.5 cm, isointense, or a ring-shaped enhancement with a hypointense center) were also assessed. Neurological findings remaining at 6-months were considered as neurological sequel.

Statistical analysis. The prognostic role of various demographic, clinical, laboratory, and radiological findings on admission in prediction of neurological sequel development were studied by multivariate logistic regression. During the evaluation of the study data, along with the descriptive statistical methods, parameters with normal distribution for the comparison of qualitative data were evaluated using Student's t-test. The qualitative data were evaluated using chi-square test and Fisher's exact test. Variables identified in univariate analysis as associated with the predictor variable were then included in the multivariate logistic regression. Initially, all the variables were included, but the best model was chosen using enter logistic regression analysis. A p-value of ≤0.05 was defined as statistically significant. All statistical analyses were performed using NCSS 2007 Statistical Software and Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah, USA).

Results. Out of 160 patients diagnosed, treated and followed up in our hospital, 2 were pregnant and one had given birth 4 months earlier. Only one patient had

HIV infection. Ninety-two percent of patients were treated with classical 4-drug therapy; the others were treated with the first line 5-drug or second line drugs. Patients with neurological deficit on admission received dexamethasone. Patients' demographic, clinical, laboratory, and cranial imaging features are summarized in **Table 1**.

Table 1 - Clinical, laboratory, and radiological findings on admission of 160 tuberculous meningitis (TBM) patients.

Characteristics	n	(%)
Age (mean ± SD)	32.18 ± 13.62	
Age range (years)	14-78	
Gender		
Male	80	(50)
Female	80	(50)
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	(15.0)
Gait abnormality	21	(13.1)
Laboratory findings		
CSF WBC count/mm³ (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	(50.0)
Positivity of culture in CSF	59	(39.9)
Radiological findings		
Chest x-ray (n=101)		
Active infiltration	36	(35.6)
Miliary	25	(24.8)
Sequels of tuberculosis	10	(9.9)
Cavitary lesion	7	(6.9)
Pleurisy	6	(5.9)
Normal	28	(27.7)
Cranial CT or MRI (n=134)		
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)

*In 8 patients infarcts were in basal ganglions (2), thalamus (1), temporal (1), insula (1), corpus callosum (1) and multiple in cerebral lobes (2); in 4 patients ischemia was in insula, thalamus, frontal lobe and multiple in cerebral lobes each

Clinical findings. The duration of TBM, the time between the first symptoms and diagnosis ranged from 2-365 days. The time from the initiation of symptoms was less than a week in 11 patients (7%), between 1-3 weeks in 91 (57%), and more than 3 weeks in 58 patients (36%). The symptoms had continued for 6 months in 2 patients and for 12 months in one patient. The antitubercular therapy was started during 1-33 days of hospitalization. The therapy was started within the first 10 days in 94% of patients. Thirty-eight percent of patients had concomitant extrameningeal TB (47 pulmonary, 6 Pott's disease, 5 lymphadenitis, 4 pleural, 2 renal, one gastrointestinal, and one skin while 6 of them had multiple site infections), 27% had previous history, and 19% had family history of TB. Diabetes mellitus, trauma, malignancy, and so forth were detected as underlying comorbidities in 37 patients (23%).

Laboratory and radiological findings. The presence of MTB in CSF was confirmed by Löwenstein-Jensen culture in 59/148 patients (40%) and by PCR in 4 patients. The investigation of the CSF samples was found negative in all patients using the India ink stain.

The erythrocyte sedimentation rate was elevated in 75%, purified protein derivative (PPD) tuberculin test was positive in 33%, and was anergic in 49% of patients. The median CSF white blood cell count was 233 (range 1-2290) and 96/148 (65%) had lymphocyte predominance. The CSF to blood glucose ratio was lower than 0.6 in 95% and 0.3 in 55% of patients. The chest radiography was abnormal in 73/101 (72%) patients and an urgent CT brain scan was carried out before or after the first lumbar puncture in available patients and then contrast-enhanced CT or MRI of the brain was performed in 136/160 patients (85%). Forty-two of tuberculomas were present on admission, and 7 developed during the therapy and were mostly multiple form and <1 cm (**Figure 1**). There was an ischemia-infarct in 12 patients' cranial CT or MRI, and they were assessed as new infarcts and associated with TBM. Cranial imaging was performed in 18/20 patients with neurological sequelae, and 2 were normal. There was a single tuberculoma in 4 patients, and multiple tuberculoma in 4 with neurological sequelae. The location of solitary lesions was infratentorial or supratentorial, and unilaterally. The diameter of these tuberculomas ranged between 3 mm and 4 cm.

Six-months follow up. The median hospitalization time of 160 TBM patients was 32 days. Fifty-six percent recovered completely, and 17% died during the hospitalization period. Most patients died within the first 10 days. There were 58 patients with major and 52 patients with minor neurological findings on admission. There were only 44 (28%) patients with neurological deficits on discharge. For determining neurological

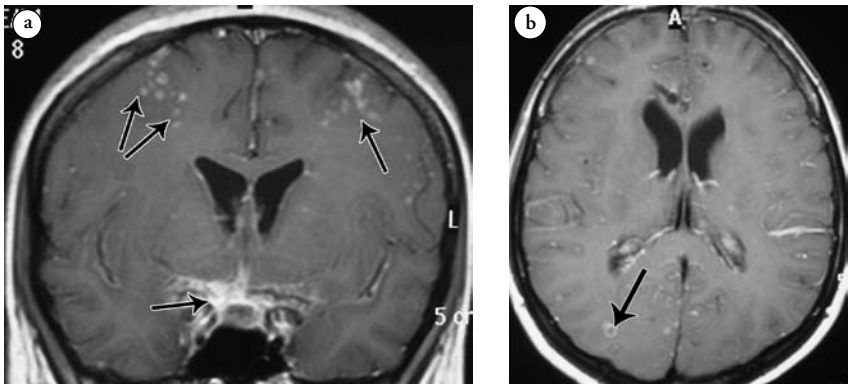

Figure 1 - Tuberculoma in the cranial MRI of a patient with tuberculous meningitis. **a)** Coronal T1-weighted with contrast enhancement MR scan shows bilateral multiple millimetric nodular parenchymal lesions (arrows) (tuberculoma). There is a dense contrast enhancement, which shows basal involvement. **b)** Axial T1-weighted with contrast enhancement MR scan shows multiple parenchymal nodular lesions (arrows).

Table 2 - The comparison of neurological findings on admission and at 6-months (N=160).

Neurological findings	On admission (n=160)	At 6-months (n=160)	
		Dead patients (n=27)	Survivors (n=133)
Altered sensorium	26	3	0
Convulsion	19	3	2
Precoma	15	8	0
Coma	11	8	0
Paresia	15	1	4
Plegia	4	0	4
Ataxia	5	0	1
Gait anomaly	4	0	1
Cranial nerve palsy	38	1	12
Optic neuritis	4	1	3
Oculomotor nerve palsy	6	0	0
Abducens nerve palsy	26	0	4
Facial nerve palsy	6	0	0
Auditory neuropathy	4	0	5
Incontinence	4	2	0
Aphasia-dysarthria	3	0	0

sequelae, 133 patients were evaluated during the 6-months after diagnoses of TBM on the basis of BI scoring. Eighty-nine patients recovered completely during the hospitalization period and none of them had a neurological sequelae during the 6-months. At the end of the 6-months period; 8 patients with major and 16 with minor neurological deficits recovered completely. Therefore, there were 20 (13%) patients, with neurological sequelae (6 with major and 14 with minor deficit) at 6-months of the clinical course. In the follow-up period, recovering rates changed to 71%, neurological sequel 13%, and death 17% at 6-months. According to the stages, the clinical outcome rates of stage I were: recovery 14.4%, mild sequel 1.9%, severe sequel 0%, and death 0%. In stage II: recovery 48.1%, mild sequel 6.2%, severe sequel 1.9%, and death 6.9%. In stage III recovery 8.1%, mild sequel 06%, severe sequel 1.9%, and death 10%.

Considering the severity rates of neurological sequel: on admission: patients without sequel comprised 31%, with minor sequel (CNP) 33%, and with major sequel (precoma, coma, convulsion, paresis-plegia, and so

Table 3 - Comparison of uni-multivariate analyses of predictors of neurological sequel in tuberculous meningitis.

Variables	Univariate analysis				Multivariate analysis			
	Odds ratio	Upper	Lower	*P*-value	Odds ratio	Upper	Lower	*P*-value
Age ≤40 years	3.15	1.14	8.69	0.022	2.94	1.00	8.59	0.049
Complaint duration 1-3 weeks	1.59	0.825	3.086	0.179	0.29	0.07	1.26	0.101
Complaint duration >3 weeks	0.91	0.441	1.891		0.32	0.07	1.44	0.139
Cranial nerve palsy	4.35	2.01	9.37	0.001	3.72	1.66	8.33	0.001
Tuberculoma	2.33	1.14	4.76	0.018	1.99	1.04	4.25	0.048
Basal meningitis	1.91	0.91	4.26	0.083	1.64	0.69	3.84	0.257

forth) 36%. On discharge: without sequel 56%, with minor sequel (CNP) 16%, and with major sequel 12%. At the sixth month: without sequel 71%, with minor sequel (CNP) 6%, with major sequel 7%.

The comparison of neurological findings on admission and at 6-months are summarized in **Table 2**. Cranial nerve palsy (12/20), hemiplegia (5/20), and paraparesis (4/20) were the most frequent neurological deficits among 20 patients with neurological sequel. Auditory neuropathy (5/12), abducens nerve palsy (4/12), and optic neuritis (3/12) were the most frequent CNP. None of 5 cases with auditory neuropathy had taken streptomycin.

Out of the 4 cases with abducens nerve palsy, one had hydrocephalus by cranial imaging. Two patients with neurological sequel had permanent seizure and a patient with optic neuritis had severe visual loss.

Eleven patients with significant hydrocephalus required neurosurgical intervention. Hydrocephalus disappeared within 4 months in 8 patients, 3 patients required a ventriculoperitoneal shunt. Twenty patients with neurological sequelae had radiographic evidence of hydrocephalus, infarct, and basal enhancement. The significant variables related to clinical outcome at 6-months of TBM on single variable analysis revealed that younger age, CNP, and tuberculoma were associated with an increased risk of neurological sequel. Finally, the best set of prognostic predictors of neurological sequel was determined as younger age (adjusted odds ratio [OR] 2.94, 95% confidence interval [CI] 1.00-8.59 p=0.049) CNP (adjusted [OR] 3.72, 95% [CI] 1.66-8.33, p=0.001) and tuberculoma (adjusted [OR] 1.99, 95% [CI] 1.04-4.25, p=0.048). The prognostic predictors derived by single and multivariable analysis are summarized in **Table 3**.

Discussion. There are many factors accepted as certain predictors of poor outcome of TBM including age, stage of illness at admission, and hydrocephalus.[3,11,12] In this study, 36.6% of patients had tuberculoma on cranial CT or MRI, and 24% of them had CNP on admission, which were found to be prognostic factors for neurological sequel in TBM course by multivariate analysis. In our study, the diagnosis of TBM was confirmed by high culture positivity in addition to the clinical and CSF findings, and neuroimaging signs. However, we concluded that, neuroimaging techniques, especially cranial MRI, are more useful than microbiological analyses for early diagnosis of TBM. In 134 patients, we performed cranial CT or MRI and the results were normal or did not support TBM in 30 patients. In this study, cranial tubercles (36.6%), basal meningitis (26.9%), leptomeningeal involvement (25.4%), and hydrocephalus (20.9%) were the most frequent neuroimaging results in accordance with previous studies.[4,5,13-15] In addition, we determined the relationship between the presence of tuberculoma and developing neurological sequel during TBM course. Tuberculosis usually involves the brain through hematogenous spread. Hematogenously disseminated MTB lodge into the corticomedullary junctions where a rupture into the subarachnoid space leads to meningeal infection and granulomatous lesions in the base cisterns. The disease occur years after the initial pulmonary infection with the reactivation of the bacillus by the hematogenous route.[16-18] A cranial granulomatous mass lesion with a hypointense core with a peripheral hyperintensity was assessed as tuberculoma.[19,20] In this study, tuberculomas were isodense or hyperdense rounded lesion that showed peripheral edema on CT/MRI scans with contrast. Intracranial tuberculoma may be seen in the form of solitary or multiple tuberculomas, but multiple tuberculomas are more common.[18,21] The neurological sequel was detected in 8/49 patients with tuberculoma (16.3%) while we detected 12/111 patients without tuberculoma (10.8%). Tuberculoma was detected in 49/160 TBM patients.

Hydrocephalus coincidence was seen in 8/49 (16%) patients with tuberculoma. This coincidence was seen only in 1/8 (13%) patients with neurological sequel. Intracranial tuberculomas were accompanied by hydrocephalus in 11-18% of TBM cases.[21,22] Our findings are in agreement with these reports. Since tuberculoma-hydrocephalus coincidence rates were similar both in patients with and without neurological sequel in this study, we suggest that the presence of hydrocephalus accompanying tuberculoma had no additive effect on developing neurological sequel. Finally, the presence of tuberculoma was detected as an independent prognostic factor on neurological sequel in the present study (p=0.048). Tuberculomas may be present anywhere in the brain, but they are mostly found in the frontoparietal region and basal ganglions.[21] Solitary tuberculoma was detected in 4 of 8 patients with neurological sequel and tuberculoma. Three of these lesions were in the cerebral hemisphere (2 in the parietal and one in the frontal region) while one was in the pons.

The time from the initiation of symptoms was less than 3 weeks in 13/20 patients with sequel, and 5/8 patients with tuberculoma and sequel. In conclusion, there were no relationship between the duration of symptoms and sequel. In addition, therapy was started within the first 3 days of hospitalization in 16 of 20 patients with sequel. According to our findings, a statistically significant correlation between the duration and sequel could not be demonstrated.

The median age was statistically lower in patients with sequel in contrast to other patients without

neurological sequel (p=0.016). Moreover, rates in patients with sequel aged <40 years were higher than patients aged >40 years (p=0.022). Finally, patients age <40 years old was detected as an important predictor, with were a significant correlation between younger age and neurological sequel in logistic regression (p=0.049). In this study, 48% of dead patients were >40 years old. The extremes of age have been reported as risk factors for death in TBM.[3,11,23] Eventually, we concluded that the younger the age, the higher rates of neurological sequel while the older the age the higher rates of mortality. Both case fatality rate and morbidity rate were low in this study (17% and 13%) and were close to those reported previously.[4,11,13,24] Organic brain syndrome, CNP, and paresis are the most frequent sequel in adults with TBM.[25] In this study, CNP (auditory neuropathy, abducens nerve palsy, and optic neuritis), hemiplegia and paraparesis were the most frequent neurological deficits among 20 patients with a neurological sequel and these findings are in accordance with previous studies.[4,25] However, altered sensorium on admission was not assessed as a predictor of neurological sequel in contrast to an important recent study.[25] Extraneural TB was reported as an independent predictor of sequel[4] and was detected on admission in 35% of our patients with neurological sequel. Cranial nerve palsy was detected in 24% on admission and 60% at the sixth month (p=0.001). Therefore, we concluded that the presence of CNP on admission was the most important prognostic factor in developing neurological sequel in TBM.

Data obtained retrospectively from the patient's hospital files were the probable limitations of this study. Some laboratory or radiological procedures may have been performed if a prospective study was designated. This study revealed that the presence of CNP on admission and tuberculoma in cranial imaging was associated with a long-term neurological sequel especially in TBM patients younger than 40-years-old. Development of neurological complications may be seen despite timely and effective anti-tuberculous therapy. So, TBM remains the most fatal and morbid form of TB.

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