A New Diagnostic Scoring for Discrimination of Tuberculous and Bacterial Meningitis on the Basis of Clinical and Laboratory Findings

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Key Words

Bacterial meningitis • C-reactive protein • Diagnostics • Tuberculosis

Abstract

Objectives: The aim of this study was to develop a new diagnostic index (DI) on the basis of clinical and laboratory findings including serum C-reactive protein (CRP) for tuberculous meningitis (TM) and bacterial meningitis (BM). **Subjects and Methods:** During a 7-year period, 96 adult patients with meningitis (30 with TM and 66 with BM) were studied retrospectively. Multivariate logistic regression analysis was performed to investigate the diagnostic value of clinical and laboratory parameters as independent predictors on discrimination of tuberculous from BM patients. **Results:** Six features predictive for diagnosis including age, CSF leukocyte count, PML dominance, length of illness, serum CRP level and blood WBC count were used. The DI model developed from these features had very high sensitivity and specificity rates of 100.0 and 95.4%, respectively. The sensitivity and specificity rates were 97.4 and 100%, respectively, in microbiologically proven cases. **Conclusion:** Our results suggested that this new DI which consists of simple clinical and laboratory parameters had the power to discriminate adult pa-

tients with documented tuberculous and BM (excluding *Brucella* meningitis). It should, however, be tested in prospective studies.

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Introduction

Meningitis is a critical disease that needs rapid diagnosis and initiation of appropriate early treatment, otherwise it could lead to permanent disabilities or death, since there is a high rate of mortality for meningitis [1–3]. Laboratory tests usually lack the power to discriminate between bacterial meningitis (BM) and non-BM [3, 4]. The etiology of meningitis is usually bacterial or viral. However, tuberculous meningitis (TM) is still one of the most important types in developing countries [5] and, in 2009, the incidence of tuberculosis in Turkey was reported as 29 per 100,000 population [6]. TM has been reported as the second or third most common form of extrapulmonary tuberculosis [7–9]. Differential diagnosis of tuberculous from BM is important for initial treatment strategies. Thwaites' diagnostic criteria was conducted for discrimination of bacterial and TM, including age, history of illness, white blood cell count, total cerebrospi-

nal fluid (CSF) white cell count and the percent of neutrophils in CSF [10]. However, this scoring method does not include the important laboratory parameter of serum C-reactive protein (CRP) level. The CRP, an acute-phase reactant, is rapidly synthesized by the liver in most invasive bacterial infections as well as in many infections and inflammations. We thought that this easy and inexpensive method might increase the sensitivity and specificity of the diagnostic criteria. Therefore, the objective of the present study was to determine a new diagnostic index (DI) using both clinical and laboratory findings, including serum CRP level for tuberculous and BM in adult patients.

Subjects and Methods

This retrospective study was performed on adult patients hospitalized with meningitis at the Infectious Disease Unit in Turgut Ozal Medical Center, Inonu University Faculty of Medicine during the period of January 2000 to June 2007. Those patients admitted with clinical and laboratory findings of tuberculous and BM with positive lumbar puncture and CRP recording within the first 24 h were included in the study. Patients with infections other than meningitis were excluded from the study because an increase in serum CRP may be related to extrameningeal infections. Patients with viral meningitis and those with no values of CRP within the first 24 h were also excluded. *Brucella* meningitis patients were also excluded from the BM group because of the chronic clinical course and similar CSF findings to TM rather than BM. Viral meningitis cases were defined as patients with a pleocytosis in the CSF, the absence of any bacterial growth on culture of the CSF, benign and acute clinical course, and no etiologic agents other than viral infection [11]. *Brucella* meningitis was defined as those patients diagnosed with CSF culture positivity and pleocytosis in CSF with standard tube agglutination test $\geq 1:160$. Clinical symptoms and signs of fever, headache, duration of illness, meningeal irritation signs, an altered level of consciousness, and neurological deficiencies were recorded. Laboratory tests from CSF (protein, glucose concentration and leukocyte counts) and blood (leukocyte counts, erythrocyte sedimentation rate, C-reactive protein) were obtained. All CSF samples were stained with Gram, India ink, Ehrlich-Ziehl-Neelsen and cultured on blood and chocolate agar and Lowenstein-Jensen media.

Patients were categorized into two subgroups according to the causative agents of tuberculous or BM. (1) TM: *Mycobacterium tuberculosis* isolated from CSF or clinical meningitis with negative Gram stain and sterile bacterial and fungal cultures plus one or more of the following: (a) cranial tomographic or cranial magnetic resonance image consistent with tuberculoma or hydrocephalus, (b) chest radiograph or chest CT consistent with miliary or active tuberculosis, and (c) good response to antituberculous treatment [1, 10]. (2) BM: A pathogenic bacteria isolated from CSF or clinical signs and symptoms of meningitis with pleocytosis in CSF and blood culture yielding a bacteria or Gram stain of CSF demonstrated a bacteriologic agent [10, 11].

Data were obtained from the patients' hospital files and computer records. Serum CRP levels were estimated by nephelometric method. There was no HIV-positive patient.

Statistical Analysis

Clinical and laboratory parameters of those who fulfilled the diagnostic criteria for bacterial and TM were compared. Normality for continuous variables was determined by the Kolmogorov-Smirnov test. As the variables did not show normal distribution ($p < 0.05$), data were expressed as the median $\pm$ interquartile ranges (IR) for continuous variables and frequency (%) for categorical variables. The differences of continuous variables between the groups were assessed using the Kruskal-Wallis test, while for categorical variables the χ^2 test (or Fisher's exact test for small proportions) was preferred.

Logistic regression analysis with a stepwise forward variable selection procedure was performed to investigate the independent effects of the determined significant variables between the groups. The cut-off times of any non-categorical variable shown to have an independent effect on predicting the diagnosis of tuberculous/BM were calculated. The final model by dichotomizing the variables and rounding the coefficients in the model were performed for determining the DI scores for each variable. The odds ratios (ORs), sensitivities, specificities, predictive values and likelihood ratios of cut-off times of total DI score were calculated; p values < 0.05 were considered significant. Statistical analyses were performed using the SPSS software version 16.0 (SPSS Inc., Chicago, Ill., USA).

Results

One hundred and forty-nine patients with meningitis were hospitalized for diagnosis and treatment. Ten patients whose serum CRP had not been obtained within 24 h after admission, 37 patients with viral meningitis and 6 *Brucella* meningitis patients were excluded. Ninety-six patients (30 TM and 66 BM) were included in the study. Patient characteristics, clinical, CSF and blood laboratory findings are shown in table 1.

In the BM group, *Streptococcus pneumoniae* ($n = 20$), *Neisseria meningitidis* ($n = 6$), *Streptococcus pyogenes* ($n = 3$), *Streptococcus* spp. ($n = 2$), *Listeria monocytogenes* ($n = 2$), *Staphylococcus* spp. ($n = 4$) and *Pseudomonas aeruginosa* ($n = 1$) were isolated from the CSF culture. Culture positivity for BM was 57.6% (38/66). The diagnosis was made on the basis of observation of any bacteriologic agents on the Gram stain of the CSF for 28 patients. *Brucella* meningitis was diagnosed by isolation of bacteria from CSF for 5 patients and standard tube agglutination test result $\geq 1:160$ for one *Brucella* meningitis patient. In the TM group, 19 (63.3%) patients were culture positive. However, 11 culture negative patients were diagnosed with radiological findings (6 with tuberculoma, 2

Table 1. Univariate analyses comparing variables between patients with TM (n = 30) and BM (n = 66)

Variables	TM	BM	p
Age, years	30 ± 27	45 ± 36	0.026
Gender, female/male	20/10	23/43	0.003
Fever	26 (86.7)	64 (97.0)	>0.05
Headache	29 (96.7)	66 (100.0)	>0.05
Loss of consciousness	18 (60.0)	51 (77.3)	>0.05
Neurological deficits	15 (50.0)	24 (36.4)	>0.05
Meningeal irritation signs	23 (76.7)	52 (78.8)	>0.05
CSF leukocyte count, cells/ml	120 ± 220	2,390 ± 5,365	0.0002
CSF protein, mg/dl	160 ± 92.5	150.5 ± 159.8	>0.05
CSF/blood glucose ratio	0.23 ± 0.19	0.21 ± 0.38	>0.05
Blood WBC, × 10 ³ /ml	10.0 ± 6.0	18.0 ± 8.8	0.0008
Serum CRP, mg/l	12 ± 18	86 ± 135	0.0004
Blood ESR, mm/h	25 ± 25	64 ± 67	0.001
Duration of illness, days	7 ± 18	2 ± 1	0.0002
Predominance of PML in CSF	4 (13.3)	60 (80.0)	0.0009
Culture positivity	19 (63.3)	38 (57.6)	>0.05

Figures are medians and interquartile ranges or numbers with percentages in parentheses.

CSF = Cerebrospinal fluid; PML = polymorphonuclear leukocytes; WBC = white blood cells; ESR = erythrocyte sedimentation rate.

with hydrocephalus in cranial MR, and 2 with miliary lesions on chest x-ray) as well as 1 patient with a good response to the antituberculous therapy.

Gender, fever, headache, loss of consciousness, neurological deficits, meningeal irritation signs, CSF protein, CSF/blood glucose ratio and ESR were excluded due to the nonsignificant results by univariate analysis (table 1).

Stepwise logistic regression analysis done to construct a diagnostic rule showed that six variables (age ≤ 56 years, duration of illness > 4 days, CSF leukocyte count ≤ 650 cells/ml, blood WBC ≤ 14 × 10³/ml, serum CRP ≤ 26 mg/l and predominance of PML in CSF < 50%) were independently associated with a diagnosis of TM. The formula for DI was derived from the final model by dichotomizing the continuous variables and rounding the coefficients in the model (table 2). The total DI was calculated for each patient according to the formula: DI score = DI (age) + DI (blood white-cell count) + DI (history of illness) + DI (cerebrospinal fluid white-cell count) + DI (cerebrospinal fluid % neutrophils) + DI (serum CRP).

The optimum cutoff for the total DI (by which to classify a patient as having TM or BM) was found by use of a ROC curve (fig. 1). The DI model developed from these features had very high sensitivity and specificity rates of 100.0 and 95.4%, respectively. Therefore, the suggested

Fig. 1. ROC curve for DI scores derived from logistic regression model with high sensitivity and specificity rates. DI > 4 = BM; DI ≤ 4 = TM (AUC = 0.995; 95% CI = 0.953–0.996; sensitivity = 100%; specificity = 95.4%; p = 0.0001).

Table 2. Weighted DI scores for dichotomized variables used for diagnosis

Variables		DI points
PMNL	≥50%	3
	<50%	0
Duration of illness	≤4 days	0
	>4 days	-3
Blood WBC	>14 × 10 ³ /ml	2
	≤14 × 10 ³ /ml	0
Serum CRP	>26 mg/l	4
	≤26 mg/l	0
Age	>56 years	2
	≤56 years	0
CSF leukocyte count	>650 cells/ml	9
	≤650 cells/ml	0

PMNL = Polymorphonuclear leukocytes; WBC = white blood cells; CSF = cerebrospinal fluid.

Diagnostic rule: If the patient has a total DI score ≤4 points, he/she has TM; if the patient has total DI score >4 points, he/she has BM.

diagnostic rule was that a total DI score of 4 or less indicated TM while a score of more than 4 indicated BM (AUC = 0.995; 95% CI = 0.953–0.996; sensitivity = 95.5%; specificity = 100.0%; $p = 0.0001$). The sensitivity and the specificity rates were 97.4% and 100%, respectively, in microbiologically proven cases. The DI scores of six *Brucella* meningitis patients were between 0 and -2 points that were calculated with the resubstitution method.

Discussion

In this study, we developed a new DI score that included serum CRP level with very high sensitivity and specificity rates (95.4 and 100.0%, respectively) for diagnosing adult TM patients. In 2002, Thwaites et al. [10] developed a DI for discrimination of bacterial and TM in a large series. They reported 97% sensitivity and 91% specificity by the resubstitution method. Their criteria included age, history of illness, white blood cell count, total cerebrospinal fluid (CSF) white cell count and the percent of neutrophils in CSF. In our new DI, we added serum CRP level because CRP usually is a helpful parameter for bacterial infections. Therefore, this new index may be called a 'Modified Thwaites' Index.

The definition of BM in our study for culture-negative patients was pleocytosis and a positive Gram stain.

Thwaites et al. [10] described the BM patient as culture-positive or recovering in 3 months without anti-tuberculous treatment and a low concentration of glucose in CSF (<50% of that in blood). However, this definition for BM may misclassify a few viral meningitis cases among BM patients.

Gram stain of CSF can certainly help to make a diagnosis of BM with a specificity approaching 100% [3, 11]. Also, low glucose level in CSF was evaluated if it was an independent parameter in our study.

Thwaites' diagnostic scoring was evaluated in a retrospective study by Sunbul et al. [12] who reported sensitivity and specificity rates of 95.8 and 71.6%, respectively. However, in microbiologically proven patients, the sensitivity decreased to 91.7% and the specificity increased to 79.7%. In our study, the new DI had a sensitivity and specificity in microbiologically proven cases of 97.7 and 100%, respectively. Adding serum CRP to this useful technique improved the power of the diagnostic score for TM from BM.

Validation of the Thwaites' diagnostic algorithm was evaluated in a study by Torok et al. [13]. The logistic regression method reported good sensitivity as 99%; however specificity was reported as 81% for differentiate adult TM patients. We recommend that our new DI be validated in prospective studies.

We did not include *Brucella* meningitis patients because the clinical course of *Brucella* meningitis is usually chronic and CSF findings can be very similar to TM. In addition, treatment of *Brucella* meningitis (selection of antibiotics and duration of treatment) is different from BM. For these reasons, we thought that including these patients in the BM group could not provide any benefit. Similarly, in a pooled analysis, Arda et al. [14] excluded *Brucella* meningitis from purulent meningitis. The DI scores of six *Brucella* meningitis patients were between -2 and 0 points, calculated with the resubstitution method. These scores were similar or close to the TM group as described: if the patient has a total DI score of 4 or less, he or she has TM. In clinical practice, this may lead to potential misclassification of *Brucella* meningitis cases in the TM group. In areas endemic for *Brucella* disease, this should be kept in mind.

Serum CRP levels have been the subject of several studies regarding the discrimination of bacterial and viral meningitis. Most of these studies were done on pediatric patients and very few included TM [15–17]. In an early study, Donald et al. [16] reported that CSF CRP levels in the BM group differed significantly from viral and TM groups. However, their study group was very small

and comprised only 11 bacterial and 9 TM cases [16]. Siri-jaichingkul et al. [18] reported significantly high serum CRP results in BM (n = 12) in Thai patients. Tuberculosis is still prevalent in developing countries and should be considered in the differential diagnosis of meningitis. Serum CRP probably should be added to the diagnostic indices for TM and BM.

In a meta-analysis, Gerdes et al. [19] reported that the CRP test discriminates well between patients with and without BM. However, the absence of analyses to show if CRP tests contributed independent diagnostic information relative to the information held in the traditionally used clinical and biochemical variables makes it difficult to evaluate the clinical usefulness of CRP tests in the management of patients suspected of having BM. The results of our study provide independent diagnostic information on the lack of knowledge on this point that was indicated by Gerdes et al. [19].

Serum procalcitonin is another protein that has been used in several studies on BM. However, it is an expensive method and using this parameter is not possible in most settings in developing countries.

The main limitation of the present study resides in its retrospective design and the small number of patients studied. However, most of the cases in both groups were confirmed microbiologically.

Conclusions

The findings of our study may provide important evidence for the utility of a DI in differentiating tuberculous from bacterial (except *Brucella*) meningitis by using simple and inexpensive clinical and laboratory parameters which can be applied easily in developing countries. Further research with prospective studies that include larger number of cases is necessary for validating this new DI.

References

- 1 Kumar R, Singh SN, Kohli N: A diagnostic rule for tuberculous meningitis. *Arch Dis Child* 1999;81:221-224.
- 2 Hosoglu S, Ayaz C, Geyik MF, Kokoglu OF, Ceviz A: Tuberculous meningitis in adults: an eleven-year review. *Int J Tuberc Lung Dis* 1998;2:553-557.
- 3 Fitch MT, van de Beek D: Emergency diagnosis and treatment of adult meningitis. *Lancet Infect Dis* 2007;7:191-200.
- 4 Michelow IC, Nicol M, Tiemessen C, Chezzi C, Pettifor JM: Value of cerebrospinal fluid leukocyte aggregation in distinguishing the causes of meningitis in children. *Pediatr Infect Dis J* 2000;19:66-72.
- 5 Sutlas PN, Unal A, Forta H, Senol S, Kirbas D: Tuberculous meningitis in adults: review of 61 cases. *Infection* 2003;31:387-391.
- 6 Refik Saydam Hygiene Center Presidency School of Public Health: The Ministry of Health of Turkey Health Statistics Yearbook 2009. Ankara, Republic of Turkey Ministry of Health, 2011.
- 7 Cagatay AA, Caliskan Y, Aksoz S, Gulec L, Kucukoglu S, Cagatay Y, Berk H, Ozsut H, Eraksoy H, Calangu S: Extrapulmonary tuberculosis in immunocompetent adults. *Scand J Infect Dis* 2004;36:799-806.
- 8 Ozbay B, Uzun K: Extrapulmonary tuberculosis in high prevalence of tuberculosis and low prevalence of HIV. *Clin Chest Med* 2002;23:351-354.
- 9 Maltezou HC, Spyridis P, Kafetzis DA: Extra-pulmonary tuberculosis in children. *Arch Dis Child* 2000;83:342-346.
- 10 Thwaites GE, Chau TT, Stepniewska K, Phu NH, Chuong LV, Sinh DX, White NJ, Parry CM, Farrar JJ: Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. *Lancet* 2002;360:1287-1292.
- 11 Brivet FG, Ducuing S, Jacobs F, Chary I, Pompier R, Prat D, Grigoriu BD, Nordmann P: Accuracy of clinical presentation for differentiating bacterial from viral meningitis in adults: a multivariate approach. *Intensive Care Med* 2005;31:1654-1660.
- 12 Sunbul M, Atilla A, Esen S, Eroglu C, Leblebicioglu H: Thwaites' diagnostic scoring and the prediction of tuberculous meningitis. *Med Princ Pract* 2005;14:151-154.
- 13 Torok ME, Nghia HD, Chau TT, Mai NT, Thwaites GE, Stepniewska K, Farrar JJ: Validation of a diagnostic algorithm for adult tuberculous meningitis. *Am J Trop Med Hyg* 2007;77:555-559.
- 14 Arda B, Sipahi OR, Atalay S, Ulusoy S: Pooled analysis of 2,408 cases of acute adult purulent meningitis from Turkey. *Med Princ Pract* 2008;17:76-79.
- 15 De Beer FC, Kirsten GF, Gie RP, Beyers N, Strachan AF: Value of C reactive protein measurement in tuberculous, bacterial, and viral meningitis. *Arch Dis Child* 1984;59:653-656.
- 16 Donald PR, Strachan AF, Schoeman JF, De Beer FC: Cerebrospinal fluid C-reactive protein in infective meningitis in childhood. *J Lab Clin Med* 1985;106:424-427.
- 17 Vaidya AK, Wagle NM, Merchant SM: Use of CSF C-reactive protein in differentiating bacterial and non-bacterial meningitis. *J Postgrad Med* 1987;33:58-60.
- 18 Siri-jaichingkul S, Tiamkao S, Sawanyawisuth K, Chotmongkol V: C reactive protein for differentiating bacterial from aseptic meningitis in Thai patients. *J Med Assoc Thai* 2005;88:1251-1256.
- 19 Gerdes LU, Jorgensen PE, Nexø E, Wang P: C-reactive protein and bacterial meningitis: a meta-analysis. *Scand J Clin Lab Invest* 1998;58:383-393.