Jpn. J. Infect. Dis., 67, 428–431, 2014

Original Article

Validation of Thwaites' Diagnostic Scoring System for the Differential Diagnosis of Tuberculous Meningitis and Bacterial Meningitis

Yan-liang Zhang[1], Su Lin[2], Ling-yun Shao[3]*, Wen-hong Zhang[3], and Xin-hua Weng[3]

[1]*Department of Infectious Diseases, Nanjing Hospital Affiliated to Nanjing Medical University, Nanjing 210006;*
[2]*Liver Center, First Affiliated Hospital of Fujian Medical University, Fuzhou 350004; and*
[3]*Department of Infectious Diseases, Huashan Hospital Affiliated to Fudan University, Shanghai 200040, China*

(Received December 1, 2013. Accepted March 6, 2014)

SUMMARY: To compare the clinical features of patients with tuberculous meningitis (TBM) and bacterial meningitis (BM) and to validate Thwaites' diagnostic scoring system for the differential diagnosis of TBM and BM, a retrospective review of 211 patients with TBM or BM who were admitted to Huashan Hospital, Fudan University, from 2007 to 2012 was conducted. The clinical characteristics and laboratory data were compared, and Thwaites' diagnostic scores were assessed at the time of admission for the differential diagnosis of TBM and BM. Significant differences were observed between the 2 groups in general information, clinical features, and cerebrospinal fluid characteristics. The sensitivity and specificity of Thwaites' diagnostic scoring system for the differential diagnosis of TBM and BM were found to be 98.2% and 43.6%, respectively, with positive and negative predictive values being 65.9% and 95.8%, respectively. The sensitivity and specificity for the differential diagnosis of TBM and initially treated BM were 98.2% and 82.9%, respectively, but were only 98.2% and 24.2% for that of TBM and partially treated BM, respectively. Thus, Thwaites' diagnostic scoring system was found to be highly effective for the differential diagnosis of TBM and initially treated BM but was found to be less effective for that of TBM and partially treated BM.

INTRODUCTION

Tuberculous meningitis (TBM) is a common infection of the central nervous system (CNS), particularly in developing countries such as China where tuberculosis is highly endemic, and is associated with high morbidity and mortality worldwide (1). Its outcome is dependent on early diagnosis and effective treatment (2,3). However, in clinical practice (4), similar clinical manifestations of TBM and bacterial meningitis (BM), particularly partially treated BM, make diagnosis rather difficult. Therefore, on the basis of clinical and routine laboratory tests, Thwaites (5) established a simple scoring system for the differential diagnosis of TBM from BM. In the current study, Thwaites' diagnostic scoring system was validated by retrospective analysis of clinical data from 211 patients with meningitis and comparison of the clinical features of patients with TBM and BM.

SUBJECTS AND METHODS

Subjects: Consent was obtained from enrolled patients before examination and treatment in accordance with the Declaration of Helsinki and the relevant laws in China. All treatments were performed considering the best interests of patients. A total of 211 consecutive patients (aged $\geq$14 years) with meningitis who were admitted to Huashan Hospital, Fudan University, between January 2007 and January 2012 were included in the study. Of these patients, 110 were diagnosed with TBM and 101 with BM. The diagnosis of TBM was based on Thwaites' diagnostic criteria (5), as follows: positive mycobacterial culture or positive acid-fast staining of the cerebrospinal fluid (CSF) or biopsy showing caseous lesions and clinical manifestations and laboratory tests consistent with meningoencephalitis; negative Gram staining, India ink preparation, acid-fast staining, culture, or biopsy. The criteria also included combination with one or more of the following conditions: (i) detection of *Mycobacterium tuberculosis* in sputum specimens, stomach flush fluid, blood preparation, urine, or lymph nodes, (ii) signs of primary or secondary pulmonary tuberculosis on chest imaging (radiography or CT scans), (iii) signs of extracranial tuberculosis on CT, magnetic resonance imaging (MRI), or ultrasound examinations, (iv) evidence of hydrocephalus, enhancement in the basal cisterns, cerebral infarction, or granuloma-like change in cranial MRI scans; and (v) efficacy of anti-tuberculosis therapy as a diagnostic test. BM was diagnosed according to the criteria established by Vibha (6). Exclusion criteria included: (i) incidence of intracranial infection secondary to CNS surgery, (ii) incidence of primary or secondary immunodeficiency disease, or (iii) a history of mental illness.

Methods: The enrolled patients, totaling 211, were subjected to standard history taking, examination, and laboratory investigations, which included biochemistry, hemogram, lumbar puncture, chest radiography, imaging of the head, and HIV screening by ELISA. Enzyme-linked immunospot assays (T-SPOT.TB), when com-

*Corresponding author: Mailing address: Department of Infectious Diseases, Huashan Hospital Affiliated to Fudan University, Shanghai 200040, China. E-mail: shaolingyundid@163.com

Table 1. Thwaites' diagnostic scoring

Parameter	DI
Age (year)	
≥36	2
<36	0
Blood WBC count (10^3/ml)	
≥15,000	4
<15,000	0
History of illness (day)	
≥6	−5
<6	0
CSF total WBC count (10^3/ml)	
≥900	3
<900	0
CSF neutrophils ratio (%)	
≥75	4
<75	0

mercially available for clinical use, were performed for 87 patients.

Thwaites' diagnostic scoring system: Thwaites' diagnostic scoring system includes 5 independent parameters: age, peripheral white blood cell (WBC) count, history of illness, total WBC count in CSF, and neutrophil ratio in CSF. The total diagnostic index (DI) was calculated for each patient according to different prefixed cut-offs. Patients with total DI values of ≤4 were diagnosed with TBM and those with values >4 with BM (Table 1).

Statistical methods: All statistical analyses were performed using SPSS17.0 software. Data are presented as mean ± standard deviation. The Student's t-test was used for comparing continuous variables between the 2 groups, and the chi-square/Fischer's exact test was used for analyzing qualitative data wherever applicable. P values of <0.05 were considered statistically significant.

RESULTS

General information: A total of 110 TBM and 101 BM patients were enrolled in this study. Nineteen patients in the TBM group (16.4%) showed positive results for mycobacterial cultures or acid-fast staining, while the remaining 91 patients were diagnosed on the basis of clinical symptoms, laboratory examination, and effects of therapy. On the other hand, 8 patients in the BM group (7.9%) showed positive results for mycobacterial cultures or Gram staining. Significant differences in age, sex, residential area, and fatality rates were not observed ($P > 0.05$) between the 2 groups. A history of illness at the time of admission in the TBM group was 31.8 ± 23.2 days, which was significantly longer compared with that in the BM group (13.4 ± 15.2 days) ($P = 0.001$); however, the BM group showed higher mean temperature at the time of admission compared with the TBM group ($P = 0.002$; Table 2).

Clinical manifestations: Fever, headache, vomiting, disturbances of consciousness, and other characteristic manifestations of CNS infection were found in most patients in both groups, but the TBM group showed higher disposition for loss of consciousness compared with the BM group (53.6% vs. 37.6%, $P = 0.027$). Physical examination revealed that positive Brudzinski's signs occurred in a significantly greater number of patients in the TBM group (46.4%) compared with the BM group (31.7%, $P = 0.035$). Laboratory examination showed that peripheral WBC count, erythrocyte sedimentation rate, and positive rate of the T-SPOT.TB test were significantly different between the 2 groups (Table 3).

Table 2. Comparisons of clinical data between TBM and BM groups

	TBM group (n = 110)	BM group (n = 101)	P value
Age (year)	43.7 ± 16.1	39.4 ± 15.9	0.052
Male, % (no.)	56.4 (62)	65.3 (66)	0.208
History of illness (day)	31.8 ± 23.2	13.4 ± 15.2	0.001
City resident, % (no.)	54.5 (60)	61.4 (62)	0.332
Temperature upon admission (°C)	37.6 ± 0.9	38.0 ± 1.0	0.002
Death rate, % (no.)	2.7 (3)	2.9 (3)	1.000

TBM, tuberculous meningitis; BM, bacterial meningitis.

Table 3. Comparisons of clinical manifestations and laboratory examinations between TBM and BM groups

	TBM (n = 110)	BM (n = 101)	P value
Fever, % (no.)	97.3 (107)	99.0 (100)	0.623
Headache, % (no.)	96.4 (106)	98.0 (99)	0.685
Vomit, % (no.)	57.3 (63)	60.4 (61)	0.676
Neck stiffness, % (no.)	74.5 (82)	66.3 (67)	0.227
Loss of consciousness, % (no.)	53.6 (59)	37.6 (38)	0.027
Hemiplegia, % (no.)	11.8 (13)	7.9 (8)	0.368
Epilepsy, % (no.)	12.7 (14)	21.7 (22)	0.100
Cranial nerve palsies, % (no.)	23.6 (26)	15.8 (16)	0.171
Kernig's sign, % (no.)	63.6 (70)	68.3 (69)	0.561
Brudzinski's sign, % (no.)	46.4 (51)	31.7 (32)	0.035
WBC count (×10^9/L)	7.5 ± 2.9	12.4 ± 6.5	<0.001
Neutrophils ratio (%)	72.7 ± 11.8	75.8 ± 11.9	0.059
ESR (mm/h)	21.8 ± 7	31.1 ± 27.5	0.014
T-SPOT.TB positive (%)	85.5 (47/55)	6.25 (2/32)	<0.001

CSF examination: WBC count, predominance of polymorphonuclear leukocytes (PMLs), levels of glucose, proteins, and chloride, and culture positivity in CSF and CSF glucose/blood glucose ratio were significantly different between the 2 groups ($P < 0.05$), unlike CSF pressure, which did not show statistically significant differences (Table 4).

Validation of Thwaites' diagnostic scoring system: Total DI was calculated for each patient on the basis of Thwaites' diagnostic scoring system. Total scores of ≤4 and >4 were obtained for 108 and 2 patients, respectively, in the TBM group. The sensitivity and specificity of Thwaites' diagnostic scoring for the differential diagnosis of TBM and BM were found to be 98.2% and 43.6%, respectively, with positive and negative predictive values being 65.9% and 95.8%, respectively. Sixty-six patients in the BM group received treatment with antibiotics for more than 3 days before admission, and these patients were referred to as the partially treated group (BM1), while the remaining 35 patients who received less than 3 days of or not received antibiotic

Table 4. Comparisons of CSF examination between TBM and BM groups

	TBM (n = 110)	BM (n = 101)	P value
Intracranial pressure (mmH_2O)	240 ± 68	228 ± 65	0.157
CSF examination			
WBC count ($\times 10^6$/L)	209 ± 204	1097 ± 4496	0.04
Predominance of PML	41.1 ± 23.7	62.5 ± 27.4	<0.001
Blood glucose (mmol/L)	2.6 ± 1.0	2.1 ± 1.1	0.001
CSF glucose/blood glucose ratio	0.42 ± 0.17	0.34 ± 0.16	<0.001
Protein (mg/L)	1877 ± 1628	1343 ± 1040	0.005
Chloride (mmol/L)	112 ± 7.9	118 ± 6.4	<0.001
Culture positivity (%)	16.4 (19)	7.9 (8)	<0.001

Table 5. Differential diagnostic values of Thwaites' diagnostic scoring for TBM and BM

	TBM (n = 110)	BM (n = 101)	BM1 (n = 66)	BM2 (n = 35)
DI ≤ 4	108	56	50	6
DI > 4	2	45	16	29
Specificity (%)		43.6	24.2	82.9
Sensitivity (%)		98.2	98.2	98.2
Positive predictive value (%)		65.9	68.3	94.7
Negative predictive value (%)		95.8	88.9	93.5

BM1, partially treated group; BM2, initially treated group.

therapy were referred to as the initially treated group (BM2). The sensitivity and specificity for the differential diagnosis of TBM and BM2 were 98.2% and 82.9%, respectively, but were only 98.2% and 24.2% for TBM and BM1, respectively (Table 5).

Therapy: Before the diagnosis of TBM, patients were administered β-lactam antibiotics such as ceftriaxone, penicillin, and piperacillin-tazobactam that have minimal effects on *M. tuberculosis*. On the diagnosis of TBM or manifestation of highly indicative symptoms, they were administered a combination of isoniazid, rifampicin, ethambutol, and pyrazinamide, which was continued for 18–24 months following discharge.

DISCUSSION

The detection of microorganisms in CSF samples by microscopy or culture techniques is crucial for the differential diagnosis of TBM and BM (7,8). However, low positive rates in these techniques render early diagnosis difficult. In the present study, the positive rates using the culture technique were only 7.9% and 16.4% in the BM and TBM groups, respectively, which is consistent with previously reported rates for *M. tuberculosis* (about 5–20%) (9,10). The improper administration of antibiotics before admission to most BM patients greatly reduce the rates of culture positivity. Moreover, harsh culture conditions and time-consuming culture operations are major bottlenecks for the early diagnosis of TBM. Although several rapid culture systems such as BACTEC and ESP have been established in recent years, their extensive use in developing countries and underdeveloped regions still remains difficult (11–13). Therefore, clinical features and routine laboratory examinations remain the chief methods for the differential diagnosis of TBM and BM (14).

BM and TBM patients usually exhibit remarkably similar clinical symptoms (7,15). In the current study, statistically significant differences in age, sex, and residential area were not observed between the 2 groups. Most patients in both groups showed characteristic symptoms of CNS infection such as fever, headache, and vomiting; however, TBM patients presented with lower body temperatures at the time of admission compared with BM patients. The TBM group was significantly more vulnerable to disturbances of consciousness than the BM group (P = 0.027), probably because most TMB patients had a longer history of illness, with some even suffering from meningoencephalitis.

A previous study showed that the sensitivity of T-SPOT.TB for TBM patients using a cut-off of 20 SFC per million mononuclear cells was 89%, which was lower than that for active pulmonary tuberculosis patients (16). In the present study, a total of 87 patients from both groups were subjected to the T-SPOT.TB test; the sensitivity and specificity of the test in the diagnosis of TBM were found to be 85.5% and 93.8%, respectively, suggesting an excellent diagnosing potential. However, only 41.2% of patients were subjected to the T-SPOT.TB test, and further studies employing a greater number of samples and the T-SPOT.TB test using CSF mononuclear cells are warranted.

Significant differences were observed between the 2 groups in CSF examination; CSF of TBM patients showed lower WBC count, PML, and chloride levels but higher glucose and protein levels and higher CSF glucose/blood glucose ratio compared with BM patients, which accorded well with previous studies (6,17). The TBM group exhibited moderate or mild fever, which usually occurred in the afternoon, for a long duration and accompanied by certain typical symptoms of tuberculosis such as anorexia, weight loss, and sleep hyperhidrosis. Moreover, several patients were diagnosed with pulmonary tuberculosis. On the contrary, the BM group typically displayed severe fever with highly elevated total peripheral WBC counts with a left shift, concomitant with CSF neutrophilic pleocytosis. MRI of the brain revealed meningeal enhancement or localized brain abscess (18,19).

Despite significant differences between the 2 groups, differentiating between them on the basis of a single clinical symptom or biochemical parameter remains a challenge. Therefore, the establishment of a diagnostic scoring system based on clinical and routine laboratory examinations is warranted. Thwaites established a scoring system employing 143 cases of TBM and 108 cases of BM by regression analysis; this scoring system was evaluated by Sunbul et al. (9) using 23 cases of TBM and 103 cases of BM; their evaluation revealed the sensitivity and specificity of the system to be 95.6% and 70.8%, respectively. The current study showed that the sensitivity of Thwaites' diagnostic scoring system for the differential diagnosis of TBM and BM was 98.2%, but its specificity was only 43.6%, which is much lower compared with previous studies (5,9). Hence, BM patients were divided into initially treated (BM2) and partially

treated (BM1) groups according to their intake of antibiotics before admission. The specificity and sensitivity of Thwaites' diagnostic scoring system for the differential diagnosis of TBM and BM2 were 82.9% and 98.2%, respectively, which is consistent with previous studies. However, the specificity in the BM1 group plummeted to 24.2%, probably because the prior intake of antibiotics partially allowed better outcomes in clinical features and CSF tests, thereby rendering the differential diagnosis more difficult.

Thwaites' diagnostic scoring system, although simple, was highly effective in the differential diagnosis of TBM and initially treated BM, but not TBM and partially treated BM. Modification of the system through the inclusion of T-SPOT.TB or MRI results is likely to render it more clinically eligible.

Acknowledgments This study was financially supported by the Health Science and Technology Development Fund of Nanjing (YKK11114). We also thank Dr. Zhen Tao (Department of Infectious Diseases, Nanjing Hospital Affiliated to Nanjing Medical University) for his great contribution to this study in data collection, analysis, and financial support.

Conflict of interest None to declare.

REFERENCES

1. World Health Organization (WHO). Global Tuberculosis Database. Geneva: WHO; 2009. Available at <http://www.who.int/research/en/.>.
2. Kalita J, Misra UK, Ranjan P, et al. Predictors of long-term neurological sequelae of tuberculous meningitis: a multivariate analysis. Eur J Neurol. 2007;14:33-7.
3. Hosoglu S, Geyik MF, Balik I, et al. Predictors of outcome in patients with tuberculous meningitis. Int J Tuberc Lung Dis. 2002;6:64-70.
4. Thwaites G, Chau TT, Mai NT, et al. Tuberculous meningitis. J Neurol Neurosurg Psychiatry. 2000;68:289-99.
5. Thwaites GE, Chau TT, Stepniewska K, et al. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. Lancet. 2002;360:1287-92.
6. Vibha D, Bhatia R, Prasad K, et al. Validation of diagnostic algorithm to differentiate between tuberculous meningitis and acute bacterial meningitis. Clin Neurol Neurosurg. 2012;114:639-44.
7. Török ME, Nghia HD, Chau TT, et al. Validation of a diagnostic algorithm for adult tuberculous meningitis. Am J Trop Med Hyg. 2007;7:555-9.
8. Moghtaderi A, Alavi-Naini R, Izadi S, et al. Diagnostic risk factors to differentiate tuberculous and acute bacterial meningitis. Scand J Infect Dis. 2009;1:188-94.
9. Sunbul M, Atilla A, Esen S, et al. Thwaites' diagnostic scoring and the prediction of tuberculous meningitis. Med Princ Pract. 2005;14:151-4.
10. Baveja CP, Gumma V, Jain M, et al. Newer methods over the conventional diagnostic tests for tuberculous meningitis: do they really help? Trop Doct. 2009;39:18-20.
11. Puccioni-Sohler M, Brandao CO. Factors associated to the positive cerebrospinal fluid culture in the tuberculous meningitis. Arq Neuropsiquiatr. 2007;5:48-53.
12. Baylan O. Culture based diagnostic methods for tuberculosis. Mikrobiyol Bul. 2005;39:107-24.
13. LaBombardi VJ. Comparison of the ESP and BACTEC systems for testing susceptibilities of *Mycobacterium tuberculosis* complex isolates to pyrazinamide. J Clin Microbiol. 2002;40:2238-9.
14. Shin SJ, Anklam K, Manning EJ, et al. Rapid mycobacterial liquid culture-screening method for *Mycobacterium avium* complex based on secreted antigen-capture enzyme-linked immunosorbent assay. Clin Vaccine Immunol. 2009;16:613-20.
15. Cunha BA. Central nervous system infections in the compromised host: a diagnostic approach. Infect Dis Clin North Am. 2001;15:567-90.
16. Patel VB, Singh R, Connolly C, et al. Cerebrospinal T-cell responses aid in the diagnosis of tuberculous meningitis in a human immunodeficiency virus- and tuberculosis-endemic population. Am J Respir Crit Care Med. 2010;182:569-77.
17. Ersoy Y, Yetkin F, Bayraktar MR, et al. A new diagnostic scoring for discrimination of tuberculous and bacterial meningitis on the basis of clinical and laboratory findings. Med Princ Pract. 2012;21:259-63.
18. Garg RK. Tuberculous meningitis. Acta Neurol Scand. 2010;122:75-90.
19. Weisfelt M, van de Beek D, Spanjaard L, et al. A risk score for unfavorable outcome in adults with bacterial meningitis. Ann Neurol. 2008;63:90-7.