

Tuberculous and brucellosis meningitis differential diagnosis

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Summary Background: The Thwaites and Lancet scoring systems have been used in the rapid diagnosis of tuberculous meningitis (TBM). However, brucellar meningoencephalitis (BME) has similar characteristics with TBM. The ultimate aim of this study is to infer data to see if BME should be included in the differential diagnosis of TBM when these two systems suggest the presence of TBM.

Method: BME and TBM patients from 35 tertiary hospitals were included in this study. Overall 294 adult patients with BME and 190 patients with TBM were enrolled. All patients involved in the study had microbiological confirmation for either TBM or BME. Finally, the Thwaites and Lancet scoring systems were assessed in both groups.

Results: The Thwaites scoring system more frequently predicted BME cases ($n = 292$, 99.3%) compared to the TBM group ($n = 182$, 95.8%) ($P = 0.017$). According to the Lancet scoring system, the mean scores for BME and TBM were 9.43 ± 1.71 and 11.45 ± 3.01 , respectively ($P < 0.001$). In addition, TBM cases were classified into "probable" category more significantly compared to BME cases, and BME cases were categorized into the "possible" category more frequently.

Conclusions: When the Thwaites or Lancet scoring systems indicate TBM, brucellar etiology should also be taken into consideration particularly in endemic countries.

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1. Introduction

Brucellosis is an endemic disease in the Mediterranean, the Balkans, the Persian Gulf, the Middle East, and in Central and South America [1–3]. Brucellar meningoencephalitis (BME) is not an infrequent form of brucellosis and is one of the leading causes of chronic CNS infections together with tuberculous meningitis (TBM) [1,4]. Although the diagnosis of BME is relatively easy [5], the diagnosis of TBM is challenging as culture is very slow and non-culture diagnostic methods lack sensitivity [6]. For this reason, two prediction systems, Thwaites and Lancet, have been developed in the rapid diagnosis of TBM. Since BME has similar characteristics with TBM [4,7,8], these two prediction systems may have the potential to misdiagnose brucellar CNS disease as TBM. The distinction of both entities is of outmost importance as the duration of therapy and types of regimens differ. In addition, the use of antituberculous medications like rifampin, quinolones or aminoglycosides, which are the major therapeutic choices in the treatment of brucellosis [1], may further complicate the course of BME due to inadequate therapeutic optimization. Therefore, we planned this multicentric study including the largest BME case series ever published to assess the place of these two prediction systems in BME and to provide comparison with TBM. To the best of our knowledge, this is the first study in literature addressing this issue. The ultimate aim of this study is to infer data if BME should be included in the differential diagnosis of TBM when these two systems suggest the presence of TBM.

2. Methods

BME and TBM patients from 35 tertiary hospitals were included in this study. A standard questionnaire was sent to the participant centers and the data were collected by using a computer database. The Institutional Review Board of Istanbul Fatih Sultan Mehmet Training and Research

Hospital approved the study protocol. Overall 294 adult patients with BME (study group) were enrolled. The inclusion criteria were all of the following: (i) the presence of clinical symptoms consistent with either meningitis or meningoencephalitis (ii) the presence of typical cerebrospinal fluid (CSF) findings consistent with meningitis, (iii) the presence of positive culture or serological tests for brucellosis in the blood or in the CSF, (iv) the absence of an alternative neurological diagnosis.

The control group comprised adult TBM patients selected from the Haydarpasa studies' database [6]. Eligible 190 TBM patients out of 507 total cases in the database with all of the parameters for Thwaites and Lancet scoring systems were enrolled. Inclusion criteria to Haydarpasa studies were clinical evidence of meningitis and microbiological confirmation of TBM. The microbiological confirmation included culture, polymerase chain

Table 1 Thwaites scoring system.

	Score
Age (years)	
≥36	2
<36	0
WBC ($10^3/\text{ml}$)	
≥15,000	4
<15,000	0
History of illness (days)	
≥6	–5
<6	0
CSF total WBC ($10^3/\text{ml}$)	
≥900	3
<900	0
CSF % neutrophils	
≥75	4
<75	0

WBC: White blood cell count; CSF: Cerebrospinal fluid.

reaction (PCR) analysis, and Ehrlich-Ziehl-Neelsen staining from the CSF.

Thwaites scoring system included five clinical and laboratory variables (Table 1). If the patient had a total score of 4 or less, the diagnosis was TBM. On the contrary, if the score was higher than 4, then the patient was classified as bacterial meningitis [9]. Accordingly, Lancet scoring system included criteria for clinical, biochemical results for CSF, cerebral imaging, and evidence of tuberculosis other than CSF (Table 2). A score of 12 was assigned as "probable", 6–11 as "possible", and less than 5 were noted as negative for TBM [10].

Since none of BME cases had acid-fast bacilli, culture or PCR positivity for tuberculosis, these cases could be classified into possible or probable categories according to Lancet scoring system. Accordingly, we included only definite TBM cases as the control group to prevent the inclusion

of meningoencephalitis other than TBM. For this reason, we checked the distribution of TBM cases for possible or probable categories, and ignored their microbiological confirmation.

SPSS 22.0 program was used for statistical calculations. Both groups were compared for Thwaites and Lancet scoring systems by using *Mann–Whitney U test*. According to the categories of both scores two patient groups were compared with *chi-square test* or *Fisher's exact test* where appropriate. The value of $p < 0.05$ was accepted as significant.

3. Results

The mean age was 36.7 ± 15.9 years and there were 135 (45.9%) females in the BME group ($n = 294$). The CSF Rose-

Table 2 Lancet scoring system.

	Score
Clinical criteria (maximum category score = 6)	
• Symptom duration of more than 5 days	4
• Systemic symptoms suggestive of tuberculosis (one or more of the following): weight loss (or poor weight gain in children), night sweats, or persistent cough for more than 2 weeks	2
• History of recent (within past year) close contact with an individual with pulmonary tuberculosis or a positive TST or IGRA (only in children <10 years of age)	2
• Focal neurological deficit (excluding cranial nerve palsies)	1
• Cranial nerve palsy	1
• Altered consciousness	1
CSF criteria (maximum category score = 4)	1
• Clear appearance	1
• Cells: 10–500 per μL	1
• Lymphocytic predominance (>50%)	1
• Protein concentration greater than 1 g/L	1
• CSF to plasma glucose ratio of less than 50% or an absolute CSF glucose concentration less than 2.2 mmol/L	1
Cerebral imaging criteria (maximum category score = 6)	
• Hydrocephalus	1
• Basal meningeal enhancement	2
• Tuberculoma	2
• Infarct	1
• Pre-contrast basal hyperdensity	2
Evidence of tuberculosis elsewhere (maximum category score = 4)	
• Chest radiograph suggestive of active tuberculosis: signs of tuberculosis = 2; miliary tuberculosis = 4	2/4
• CT/MRI/ultrasound evidence for tuberculosis outside the CNS	2
• AFB identified or <i>Mycobacterium tuberculosis</i> cultured from another source-i.e., sputum, lymph node, gastric washing, urine, blood culture	4
• Positive commercial <i>M. tuberculosis</i> NAAT from extra-neural specimen	4
Exclusion of alternative diagnoses	
An alternative diagnosis must be confirmed microbiologically (by stain, culture, or NAAT when appropriate), serologically (e.g., syphilis), or histopathologically (e.g., lymphoma). The list of alternative diagnoses that should be considered, dependent upon age, immune status, and geographical region, include: pyogenic bacterial meningitis, cryptococcal meningitis, syphilitic meningitis, viral meningoencephalitis, cerebral malaria, parasitic or eosinophilic meningitis (<i>Angiostrongylus cantonesis</i> , <i>Gnathostoma spinigerum</i> , toxocariasis, cysticercosis), cerebral toxoplasmosis and bacterial brain abscess (space-occupying lesion on cerebral imaging) and malignancy (e.g., lymphoma)	

TST: Tuberculin skin test. IGRA: Interferon-gamma release assay. NAAT: Nucleic acid amplification test. AFB = acid-fast bacilli. The individual points for each criterion (one, two, or four points) were determined by consensus and by considering their quantified diagnostic value as defined in studies.

WBC: White blood cell count; CSF: Cerebrospinal fluid.

Table 3 Mean, median values and categorical classification of Thwaites scores.

	Study group (Neurobrucellosis) n = 294	Control group (TBM) n = 190	p
Median score (IQR)	-3 (-5 to -3)	-3 (-5 to 0)	0.001^a
Mean $\pm$ SD score	-3.11 $\pm$ 2.30	-2.09 $\pm$ 3.11	
Diagnostic classification			0.017^b
TBM	292 (99.3%)	182 (95.8%)	
Bacterial meningitis	2 (0.7%)	8 (4.2%)	

TBM: Tuberculous meningitis, IQR: Interquartile range.

P < 0.05 are significant in bold.

^a Mann-Whitney U test.^b Fisher's exact test.**Table 4** Mean, median values and categorical classification of Lancet scores.

	Study group (Neurobrucellosis) n = 294	Control group (TBM) n = 190	p
Median score (IQR)	10 (9–10)	11 (10–14)	< 0.001^a
Mean $\pm$ SD score	9.43 $\pm$ 1.71	11.45 $\pm$ 3.01	
Diagnostic categories			< 0.001^b
Probable	26 (8.8%)	86 (45.3%)	
Possible	259 (88.1%)	98 (51.6%)	
Negative for TBM	9 (3.1%)	6 (3.2%)	

TBM: Tuberculous meningitis, IQR: Interquartile range.

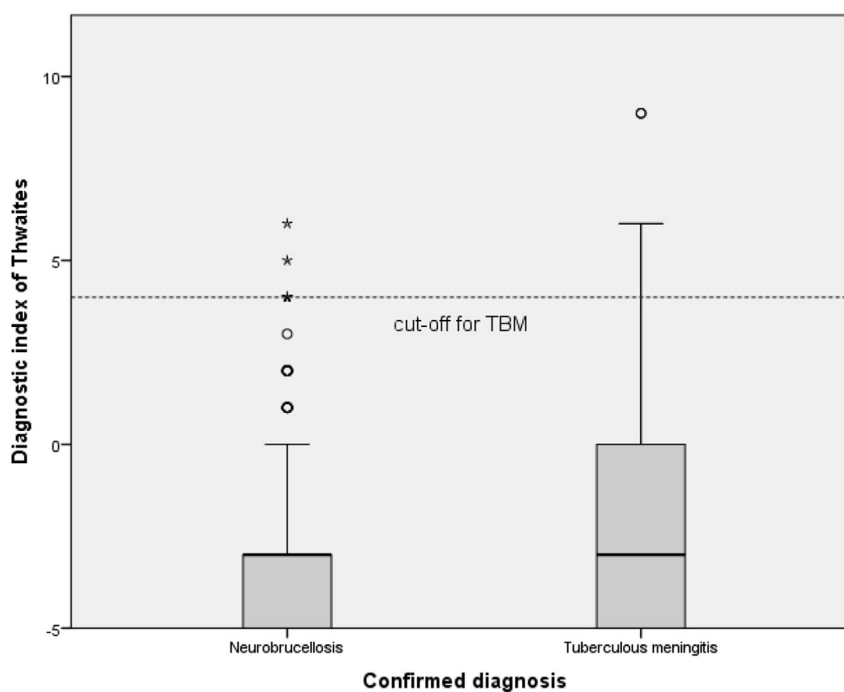
P < 0.05 are significant in bold.

^a Mann-Whitney U test.^b Chi-square test.

Bengal was positive in 98/151 (64.9%) of the patients. The CSF tube agglutination test was positive in 200/237 (84.4%) patients and in 59/65 (90.7%) cases the CSF Coombs agglutination test was positive. In 39/264 (14.7%) cases *Brucella* spp were recovered from the CSF culture while the microorganism was isolated from the blood in 74/275 (26.9%) cases. The CSF PCR was found to be positive in 3/27 (11.1%) BME patients. In the TBM group (n = 190), the mean age was 41.1 $\pm$ 19.7 years and there were 91 (47.9%) females. Acid-fast bacilli were shown in 40 (21%) cases while *Mycobacterium tuberculosis* was recovered in 139 (73.2%) patients from the CSF. CSF PCR was positive for *M. tuberculosis* in 39 cases (20.5%).

The mean and median values of Thwaites scores are presented in Table 3. The Thwaites scoring system more frequently predicted BME cases (n = 292, 99.3%) compared to the TBM group (n = 182, 95.8%) (P = 0.017). Comparison of the diagnostic index of Thwaites between BME and TBM are shown in Fig. 1.

According to the Lancet scoring system, the mean scores for BME and TBM were 9.43 $\pm$ 1.71 and 11.45 $\pm$ 3.01 respectively (P < 0.001). Added to that, TBM cases were classified into "probable" category more significantly compared to BME cases, and the latter was categorized

**Figure 1** Comparison of the diagnostic index of Thwaites between brucellar meningoencephalitis and tuberculous meningitis.

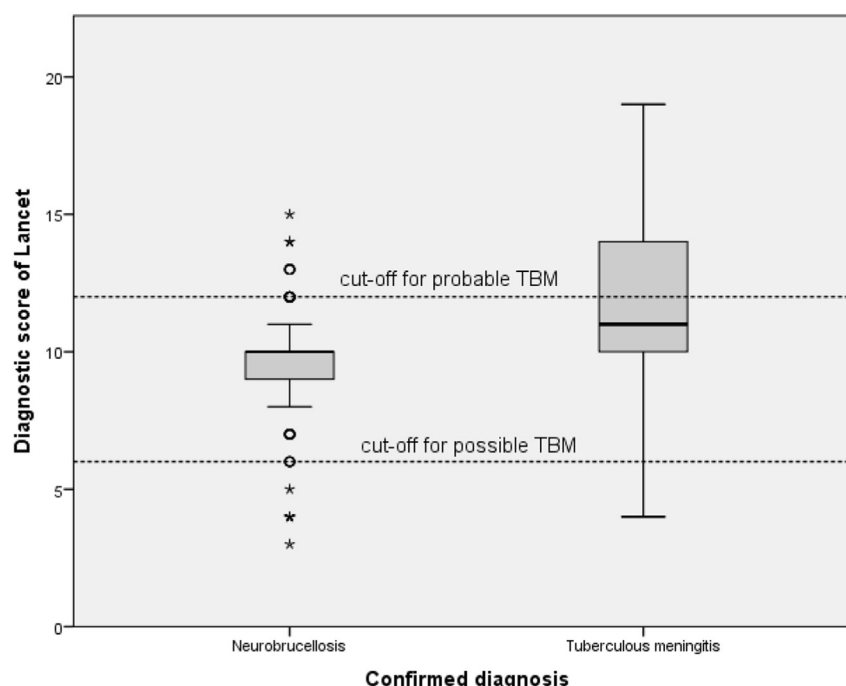


Figure 2 Comparison of Lancet diagnostic score for brucellar meningoencephalitis and tuberculous meningitis.

into possible category more frequently (Table 4). Comparison of Lancet diagnostic scores for BME and TBM is shown in Fig. 2.

4. Discussion

Brucellosis and tuberculosis are multisystemic diseases, which both may present with a broad spectrum of clinical manifestations and complications. BME is observed in 3–6% of all brucellosis patients [11–13] while TBM is reported in up to 1% of all tuberculosis cases [14]. One of the most important differentials for neurobrucellosis in resource poor settings is considered to be tuberculosis by the clinicians [15]. Both diseases have extensively variable neurologic manifestations, including meningitis, meningoencephalitis, cranial nerve involvement, myelitis, radiculopathy, neuropathy, depression, paraplegia, stroke, and abscess formation [4,7,8,16–18]. Thus, microbiological diagnosis in both CNS infections is a great focus of concern in medical practice [5,6]. The issue is more complicated in brucellosis endemic countries, which mostly comprise developing world with limited diagnostic capacity. Thus, Thwaites and Lancet scoring systems produced to predict TBM are widely used by clinicians to aid diagnosis. The former is a simplified scale including five parameters on the basis of clinical and laboratory features [9]. Alternatively, the latter is a relatively more complex scale comprising clinical, cerebrospinal, imaging, and laboratory data [10]. Although the Lancet and Thwaites' diagnostic scoring systems were found to be highly effective in the differential diagnosis of TBM and bacterial meningitis in previous studies [19–21], the agreement between these two scores was not strong [21]. Our data disclosed that these two prediction systems falsely identified

BME patients as TBM. Furthermore, the Thwaites scoring system identified BME patients as TBM significantly higher than TBM patients. Nevertheless, the Lancet scoring system indicated the majority of BME cases to be in the "possible" category and only 9% of the cases were classified into "probable" TBM category in our study.

BME frequently has a subtle nature and cannot be suspected easily due to its silent course [7]. Although the mortality is around 1% with treatment, one-fifth of the cases experiences persistent sequelae despite all therapeutic efforts [4]. There are no scoring systems available for BME. Thus, the clinician should use every microbiological diagnostic modality available to them to diagnose BME when the Thwaites or Lancet prediction system suggests TBM. The highest sensitivity in the diagnosis of BME is the serological tests [5,22] and the use of automated culture system for CSF samples is better than the solid media in the diagnosis. Furthermore, blood cultures should be immediately obtained [5].

Although the major limitation of this study is its retrospective design, it is very difficult to provide such large cohorts prospectively for BME and TBM. In conclusion, when Thwaites or Lancet scoring systems predicts TBM, brucellar etiology should be immediately taken into consideration particularly in brucellosis endemic countries.

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Conflict of interest

None to declare.

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