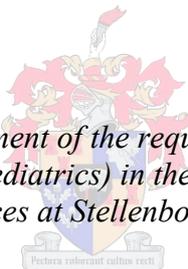


Clinical value of a uniform research case definition of tuberculous meningitis

By
Marie Wessels

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Supervisor: Dr Regan Shane Solomons

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DECLARATION

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ABSTRACT

BACKGROUND: Tuberculous meningitis (TBM) research remains important but obtaining adequate sample sizes of microbiologically-confirmed TBM cases is difficult, therefore clinical cases of TBM need to be included. A uniform research case definition for TBM was developed to assist diagnostic standardization.

METHODS: Our study evaluated the proposed uniform research case definition in a group of children diagnosed with TBM. A subgroup of 66 children with culture-confirmed TBM was compared to culture-confirmed bacterial meningitis controls.

RESULTS: The uniform case definition was applied to 554 TBM patients. Sixty-six (11.9%) patients had definite TBM, 408 (73.6%) had probable TBM and 72 (13.0%) had possible TBM. Symptom duration >5 days, weight loss or persistent cough >2 weeks, recent TB contact, focal neurological deficit, clear cerebrospinal fluid (CSF) appearance and basal meningeal enhancement predicted TBM when compared to definite bacterial meningitis with a sensitivity and specificity of 97.0% and 93.7%, respectively. When using a probable TBM score as the diagnostic measure, sensitivity was 86% and specificity was 100%. When using a possible TBM score as the diagnostic measure, sensitivity was 100% but specificity was 56%.

CONCLUSION: The uniform research case definition for TBM performed well when using a probable TBM score as the diagnostic marker. A regression model also differentiated TBM from bacterial meningitis with good accuracy, but caution is needed in its application to early TBM.

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CONFLICT OF INTEREST

The author does not have to declare a conflict of interest.

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	Diagnostic score	Definite TBM n(%)	Probable TBM n(%)	Possible TBM n(%)	Definite BM n(%)
Staging: I		2(3)	5(1)	4(6)	n/a
IIa		35(53)	214(52)	47(65)	n/a
IIb		2(3)	16(4)	1(1)	n/a
III		27(41)	172(42)	18(25)	n/a
Clinical criteria (Max category score=6)					
Symptom duration > 5 days	4	47(71)	366(90)	40(56)	6(19)
>1 of: poor weight gain/weight loss, night sweats or persistent cough >2 weeks	2	31(47)	204(50)	25(35)	1(3)
History of recent TB contact or positive TST or IGRA	2	33(50)	291(71)	36(50)	2(6)
Focal neurological deficit	1	33(50)	286(70)	27(38)	2(6)
Cranial nerve palsy	1	18(27)	110(27)	17(24)	2(6)
Altered consciousness	1	46(70)	398(98)	65(90)	19(59)
CSF criteria (Max category score=4)					
Clear appearance	1	66(100)	408(100)	72(100)	18(56)
Cells: 10–500 per µl	1	55(83)	361(88)	56(78)	20(63)
Lymphocytic predominance (>50%)	1	51(77)	326(80)	53(74)	19(59)
Protein concentration >1 g/L	1	49(74)	292(72)	42(58)	15(47)
CSF to plasma glucose ratio <50%	1	47(71)	263(64)	34(47)	17(53)
Cerebral imaging criteria (Max category score=6)					
Hydrocephalus	1	63(96)	353(87)	51(71)	9(28)
Basal meningeal enhancement	2	48(73)	318(78)	19(26)	1(3)
Tuberculoma	2	5(8)	55(13)	5(7)	1(3)
Infarct	1	15(23)	142(35)	3(4)	3(9)
Pre-contrast basal hyperdensity	2	No data	No data	No data	0(0)

Evidence of tuberculosis elsewhere (Max category score=4)					
Chest Xray suggestive of active TB	2	26(3)	206(50)	17(24)	3(9)
Chest Xray suggestive of miliary TB	4	11(17)	53(13)	1(1)	0(0)
CT/ MRI/ US evidence for TB outside CNS	2	0(0)	0(0)	0(0)	0(0)
positive extraneural M.tb microscopy/culture	4	19(29)	100(25)	2(3)	0(0)
Positive extraneural commercial NAAT	4	No data	No data	No data	0(0)
Exclusion of alternative diagnoses					
An alternative diagnosis must be confirmed microbiologically, serologically or histopathologically					
Definite TBM = CSF: AFB on microscopy, positive M.tb culture, or a positive commercial NAAT					
Probable TBM = total score of ≥ 12 when neuroimaging available = total score of ≥ 10 when neuroimaging unavailable					
Possible TBM = total score of 6-11 when neuroimaging available = total score of 6-9 when neuroimaging unavailable					

TBM= tuberculous meningitis, BM= bacterial meningitis, TB= tuberculosis,

TST=tuberculin skin test, IGRA=interferon gamma-release assay, CSF= cerebrospinal

fluid, CT= computed tomography, MRI= magnetic resonance imaging, US= ultrasound,

AFB= acid-fast bacilli, *M.tb*= Mycobacterium tuberculosis, NAAT= nucleic acid

amplification test

Table 2. Findings on univariate analysis when comparing definite TBM to definite bacterial meningitis. Relative risk, 95% confidence interval and p values are shown.

	OR (95% CI)	p value
Symptom duration > 5 days	10.7 (3.8-30.2)	0.000
Weight loss or persistent cough > 2 weeks	27.5 (3.5-213.1)	0.002
Recent close TB contact or pos TST/IGRA	15.0 (3.3-67.9)	0.000
Focal neurological deficit	15.0 (3.3-67.9)	0.000
Cranial Nerve Palsy	5.6 (1.2-26.0)	0.027
Altered level of consciousness	1.6 (0.7-3.8)	0.312
Clear CSF appearance	50.6 (6.2-410.7)	0.000
CSF cells 10-500/ μ l	3.0 (1.1-7.9)	0.260
Lymphocyte predominance >50%	1.6 (0.6-4.0)	0.366
Raised protein >1g/L	3.3 (1.4-7.9)	0.009
CSF:serum glucose ratio <50%	2.2 (0.9-5.2)	0.080
Hydrocephalus	53.7 (13.4-215.7)	0.000
Basal meningovascular enhancement	82.7 (10.5-651.0)	0.000
Tuberculoma	2.5 (0.3-22.7)	0.404
Infarct	2.8 (0.8-10.7)	0.121
CXR suggesting active TB	6.3 (1.7-22.8)	0.005
CXR suggesting military TB	6.2 (0.8-50.3)	0.088
Positive extraneural M.tb microscopy and/or culture	12.5 (1.6-98.5)	0.016

OR= odds ratio, CI= confidence interval, TB= tuberculosis, TST=tuberculin skin test, IGRA=interferon gamma-release assay, CSF= cerebrospinal fluid, CXR= chest X-ray, AFB= acid-fast bacilli

Table 3. Multivariable logistic regression analysis

	OR	95% CI		p-value
Symptom duration >5 days	14.12	3.59	55.50	0.000
Weight loss or persistent cough > 2weeks	55.07	5.71	530.92	0.001
Recent close TB contact or pos TST/IGRA	18.99	3.22	111.95	0.001
Constant	0.148			0.000

OR=odds ratio, CI=confidence interval, TB= tuberculosis, TST=tuberculin skin test,

IGRA=interferon gamma-release assay

CONTENT

Introduction

Tuberculosis (TB) remains a global health problem with a high morbidity and mortality, despite effective anti-tuberculous medication. Although the situation has improved in many areas, the absolute numbers are unchanged.^{1,2} TBM is the most devastating manifestation of TB, mostly due to delayed diagnosis from non-specific early symptoms such as cough, loss of weight, fever, vomiting and malaise. With disease progression, a more definitive clinical picture becomes manifest.³ Early initiation of treatment, and therefore early diagnosis of TBM, is the most critical factor affecting morbidity and mortality.^{4,5}

Culture of *Mycobacterium tuberculosis* (*M.tuberculosis*) from cerebrospinal fluid (CSF) provides a definitive criterion for TBM diagnosis. TBM is paucibacillary, resulting in low sensitivity (10-20%) of CSF microscopy for acid-fast bacilli.⁶ Culture of CSF has a poor sensitivity of less than 50%^{3,7,8} and can take up to 42 days to provide a positive result. A meta-analysis of the accuracy of nucleic acid amplification tests (NAATs) for the diagnosis of TBM showed that commercial NAATs had a sensitivity of 56% and a specificity of 98%, and although providing a definite diagnosis, it is a poor 'rule out' test.⁹

There are still many unanswered questions regarding TBM treatment.¹⁰ A recent international health review found that existing trials assessing anti-tuberculous treatment for TBM had limited power, poor methodology and used varying treatment regimens

with conflicting results. Ideally, multi-centre randomized controlled trials are required, standard diagnostic and staging criteria should be applied and sufficient numbers should be recruited to demonstrate differences in outcome.¹¹ As it is difficult to obtain adequate sample sizes using microbiologically confirmed TBM cases, probable and possible clinical cases of TBM need to be included.

Recently, a uniform research case definition for TBM in adults and children was developed to achieve standardization of diagnosis for research purposes,¹² but it would be useful if this definition could also be applied in clinical settings. The research tool defines TBM as definite if acid-fast bacilli are visualized and/or culture of *M.tuberculosis* from CSF is obtained and/or a commercial NAAT is positive. The clinical diagnosis of probable or possible TBM is based on clinical findings and special investigations. The boundaries between groups are not fixed, and patients can move between groups.

Patients must have a clinical diagnosis of meningitis before the uniform research case definition can be applied. A scoring system then determines whether a patient falls in the probable or possible TBM category (Table 1). The scoring system was based on literature review of diagnostic algorithms for TBM in adults and/or children, expert experience and consensus decision.¹³⁻¹⁷ The threshold for inclusion should not be too high to exclude stage I TBM cases as this is the group with best outcome, but sometimes is the most difficult in which to make a diagnosis.

Our study tests this uniform research case definition on a group of children diagnosed with, and treated for, TBM in a tertiary care hospital.

Patients and methods

The aim of this study was to test a recently proposed research case scoring system¹² by application of the scoring systems to a clinical case series of 554 children under age 13 years, fulfilling a case definition of TBM, that were prospectively collected between January 1985 and April 2005. Within this case series, a subgroup of 66 children with culture-confirmed (definite) TBM was identified, and compared to a control group with culture-confirmed (definite) bacterial meningitis. Thirty-two children, aged <13 years, and diagnosed between 2003 and 2009 were identified from the National Health Laboratory Service database. The study was conducted at Tygerberg Children's Hospital, Cape Town, the tertiary academic hospital of the Faculty of Medicine & Health Sciences, Stellenbosch University. The study was approved by the Human Research Ethics Committee of Stellenbosch University, Cape Town, Western Cape, South Africa (ethics nr. N10/11/367).

Definitions

Definition of definite TBM

A diagnosis of definite TBM was made if acid-fast bacilli were identified on CSF microscopy and/or *M.tuberculosis* was cultured from CSF.

Case definition of TBM

A diagnosis of probable TBM was made when 2 or more of the following criteria were

present in the setting of a characteristic history and CSF changes associated with TBM: a positive history of contact with an adult TB case, a positive tuberculin skin test, a chest x-ray suggestive of pulmonary tuberculosis (hilar lymphadenopathy, miliary tuberculosis or cavitation), computed tomography (CT) or magnetic resonance imaging (MRI) demonstrating features of TBM (hydrocephalus, meningovascular enhancement and/or granuloma/s), poor weight gain and positive microbiological identification of acid-fast bacilli from gastric washings.³

Definition of definite bacterial meningitis

A diagnosis of definite bacterial meningitis was made if bacterial pathogens were identified by Gram stain and/or culture from CSF.

Scoring¹²

Table 1 illustrates the diagnostic scoring criteria used. Points are allocated in the following categories: 1) clinical findings 2) CSF results 3) neuroimaging findings 4) evidence for TB outside the central nervous system and 5) additional laboratory criteria. A total score of at least 12 is compatible with probable TBM (when neuroimaging is unavailable, the total score is reduced to at least 10), while a total score of 9-11 equates to a possible TBM diagnosis (when neuroimaging is unavailable the total score required is reduced to 6-9). A certain number of points have to come from the CSF or neuroimaging criteria to ensure that the patient is indeed suffering from meningitis and not some other chronic type of tuberculosis. It was suggested by the consensus group that alternative causes for the clinical presentation must be excluded by means of the following CSF investigations: 1) Gram stain and bacterial culture 2) India ink stain,

cryptococcal antigen latex agglutination test and cryptococcal culture 3) investigations to exclude neurosyphilis 4) cerebral malaria investigations in endemic areas 5) viral culture and polymerase chain reaction (PCR) if clinically indicated. Due to the retrospective nature of the study, the following diagnostic criteria could not be evaluated: pre-contrast basal hyperdensity on CT, CT/MRI/Ultrasound imaging of TB outside the CNS and positive polymerase chain reaction (PCR) evidence of extra-neural TB.

The stage of TBM in each patient was also determined as follows: Stage I) Glasgow Coma Scale (GCS) of 15 and no focal neurology Stage IIa) GCS of 15 plus focal neurology Stage IIb) GCS of 11-14 with focal neurology Stage III) GCS <11.^{17,18}

Statistical analysis

The Statistical Package for the Social Sciences version 19 (SPSS Inc, Chicago, IL, USA) and SAS (Statistical analysis system) version 9.1 (SAS Institute Inc., Cary, North Carolina, USA) was used for statistical analysis. Frequencies of the scoring criteria in the case-definition TBM and bacterial meningitis groups were obtained. We used the Fishers-exact test and odds ratios in univariate analyses to compare the definite TBM group and the definite bacterial meningitis control group. Two-tailed statistical significance was determined at $p < 0.05$. To study the independent effect of variables, multivariate logistic regression analysis was used. Variables in the uniform research case definition were included, step-wise, in a multivariate logistic regression model, for which statistical significance was set at the 5% level. A receiver operating characteristic (ROC) curve was constructed. The area under the curve (AUC) was used to distinguish between patients with definite TBM and definite bacterial meningitis. An AUC of > 0.70 is generally considered to be adequate for determining accuracy.

Results

To enter the TBM study group, children had to fulfill the probable case definition for TBM. All 554 patients fulfilled these criteria. The uniform case definition was then applied. According to the uniform research case definition criteria, 66 (11.9%) patients had definite TBM, 408 (73.6%) had probable TBM and 72 (13.0%) had possible TBM. Eight patients scored as unlikely TBM. Out of this last subgroup, 3 patients had no CSF or neuroimaging investigations, 2 had no CSF investigations, and the remaining three patients had poor clinical criteria scores. Table 1 shows the diagnostic criteria frequency for each of the above groups. Only 8 out of the 554 patients with TBM, were HIV-infected. Two-hundred and five patients in this study were HIV-negative; in 341 patients, the HIV status was unknown. HIV prevalence was low during the earlier years of the 20-year period that the patients were recruited.

In the possible TBM group, 25% of patients were stage III, compared to 42% and 41% in the probable and definite TBM groups respectively. This shows that disease severity at onset (staging) is more severe in the probable/definite group compared to the possible group.

When scoring the patients independent of culture confirmation i.e. either as probable TBM, possible TBM or no TBM, the definite TBM group of 66 included 57 scoring as probable TBM and 9 scoring as possible TBM. The definite bacterial meningitis group of 32 included 18 scoring as no TBM, but 14 scoring as possible TBM. When using a probable TBM score as a positive diagnostic test marker, sensitivity was 86% and

specificity was 100%. When the denominator was lowered to a possible TBM score, sensitivity was 100% and specificity was 56%.

Table 2 summarizes the univariate analysis of criteria in the uniform research case definition, when comparing definite TBM to definite bacterial meningitis. Variables in the uniform research case definition were entered step-wise in a multivariable logistic regression analysis model. All variables with $p < 0.10$ were inserted in the model. It was also decided to keep duration of illness > 5 days ($p = 0.115$) and weight loss and/or persistent cough longer than 2 weeks ($p = 0.105$) in the model (Table 3). The overall specified group percentage is 95.9% with a cut off of 50%, meaning that 95.9% of inclusions were correctly predicted by the statistical model used. The AUC of the constructed ROC curve (Figure 1) was 0.990 (95% confidence interval: 0.957–0.982) and at the cut point at the furthest left hand corner of the ROC curve, the sensitivity was 97.0% and specificity 93.7%.

Discussion

TBM often presents with non-specific symptoms in stage I of the disease. It is precisely this period where the diagnosis needs to be made, as morbidity and mortality increases exponentially with disease progression. Stage I TBM, left untreated can progress to stage II, or even stage III within a short time. Therefore the need for rapid diagnosis, in order to initiate treatment at the earliest opportunity.

However, ‘gold standard’ diagnosis of TBM is difficult, even in resource-sufficient settings. Microscopic detection of acid-fast bacilli has low sensitivity and is difficult due

to the paucibacillary nature of TBM⁵. Culture of *M.tuberculosis* on CSF also has unimpressive sensitivity and is time-consuming⁸⁻¹⁰, in a disease where a few days can make a significant difference and *M.tuberculosis* PCR on CSF, even though it holds promise, has low sensitivity¹¹. There is definitely still a need, therefore, for combination of clinical, laboratory and neuroimaging criteria for early identification of TBM suspects, and early treatment initiation. We obtained good sensitivity and specificity for our condensed version of the uniform research case definition for TBM, compared to available diagnostic methods.

In previous studies comparing TBM and bacterial meningitis, five features were predictive of a diagnosis of TBM: age, length of history, headache, white blood cell count, clear CSF appearance, total CSF white cell count, low CSF neutrophil proportion, and elevated CSF protein.^{13,16} Good sensitivities and specificities were obtained using both a composite clinical reference standard, and when applied to a microbiologically proven *M.tb* reference standard.¹⁴ Our study only used clear CSF appearance in common with previous studies when predicting TBM vs bacterial meningitis.

The study was limited by absence of data regarding pre-contrast basal hyperdensity, suggestive CT, MRI or ultrasound imaging of TB outside the CNS and positive polymerase chain reaction (PCR) evidence of extra neural TB. Pre-contrast basal hyperdensity was described only in 2004 and was therefore not available.¹⁹ Univariate analysis showed that the majority of criteria were associated with a diagnosis of definite TBM. All of the scoring criteria have been shown to delineate TBM in different studies, therefore were included in the research algorithm¹³. A set of six criteria; symptom duration >5 days, weight loss or persistent cough >2 weeks, recent TB contact, focal neurological deficit, clear CSF appearance and basal meningeal enhancement were included in the multivariate logistic regression model and good sensitivity and specificity

was obtained when predicting TBM.

The proposed uniform research case definition, even though untested, was an attempt to improve methodology, compare data and encourage collaboration. The criteria in the algorithm was based on literature review and expert opinion.¹² Our study found that when using a probable TBM score as a diagnostic marker against a 'gold standard diagnosis of TBM, a sensitivity of 86% and 100% was obtained. This compared well to the regression model, with a lower sensitivity but perfect specificity. However, when using a possible TBM score as the diagnostic marker, the specificity was wholly inadequate. Even though the group of possible TBM is a grey area, with a number of false positives, the 100% sensitivity is encouraging, as the aim is precisely to start all children with TBM on early anti-tuberculous therapy. Reviewing the points allocated to criteria and groups in the research case definition needs to be looked at in future studies, as well as testing the criteria with larger sample sizes.

The uniform research TBM case definition needs to be tested robustly in future prospective studies including bacterial meningitis, viral meningitis and normal CSF control groups, and in both adult and pediatric populations.

It is important to appreciate that the diagnostic research criteria were not designed for use in clinical practice. The normal examination findings in stage I TBM is a limitation of the diagnostic criteria. It would therefore be less likely to score as probable TBM at an earlier stage of disease. The uniform case definition holds promise, especially in resource-constrained settings with limited diagnostic availability, until better rapid diagnostic testing becomes available. Larger prospective studies where the uniform case definition is robustly tested need to be performed.

Conclusion

The uniform research case definition for TBM performed well when using a probable TBM score as the diagnostic marker, but less well when including possible TBM scores. Rigorous data collection needs to be ensured in order that information is obtained in all criterion categories in the case definition. The set of 6 criteria predicted by the regression model also had good accuracy when differentiating TBM from bacterial meningitis, and could easily be applied in clinical practice, but care should be exercised in applying this definition as a clinical diagnostic aid, particularly with regard to suspected TBM.

REFERENCES

(manually inserted)

1. World Health Organization. *Global Tuberculosis Report*. WHO report 2012. Geneva, Switzerland.
2. World Health Organization. *Global Tuberculosis Control; Epidemiology, Strategy and Financing*. WHO report 2011. Geneva, Switzerland.
3. van Well GT, Paes BF, Terwee CB, et al. Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the Western Cape of South Africa. *Pediatrics*. 2009;123(1):1-8.
4. Schoeman JF, Wait J, Burger M, et al. Long-term follow-up of childhood tuberculous meningitis. *Dev Med Child Neurol*. 2002;44:522-6.
5. Garg RK. Tuberculosis of the central nervous system. *Postgrad Med J*. 1999;75:133-140.
6. Thwaites G, Chau TTH, Mai NTH, et al. Tuberculous meningitis. *J Neurol Neurosurg Psychiatry*. 2000;68:289-99
7. Jönsson B, Ridell M. The Cobas Amplicor MTB Test for Detection of Mycobacterium tuberculosis Complex from Respiratory and Non-respiratory Clinical Specimens. *Scand J Infect Dis*. 2003;35(6-7):372-7.
8. Hosoglu S, Geyik MF, Balik I, et al. Predictors of outcome in patients with tuberculous meningitis. *Int J Tuberc Lung Dis*. 2002;6(1):64-70.
9. Pai M, Flores LL, Pai N, et al. Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2003;3:633-43.
10. Thwaites GE, Tran TH. Tuberculous meningitis: many questions, too few answers. *Lancet Neurol* 2005;**4(3)**:160-70.

11. Wolbers M, Heemskerk D, Chau TT, et al. Sample size requirements for separating out the effects of combination treatments: randomised controlled trials of combination therapy vs. standard treatment compared to factorial designs for patients with tuberculous meningitis. *Trials*. 2011;**12**(1):26.
12. Marais S, Thwaites GE, Schoeman JF, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. *Lancet Infect Dis*. 2010;10(11):803-12.
13. Youssef FG, Afifi SA, Azab AM, et al. Differentiation of tuberculous meningitis from acute bacterial meningitis using simple clinical and laboratory parameters. *Diagn Microbiol Infect Dis*. 2006; 55:275–8.
14. Moghtaderi A, Alavi-Naini R, Izadi S, Cuevas LE. Diagnostic risk factors to differentiate tuberculous and acute bacterial meningitis. *Scand J Infect Dis*. 2009;41:188–94.
15. Sunbul M, Atilla A, Esen S, et al. Thwaites' diagnostic scoring and the prediction of tuberculous meningitis. *Med Princ Pract*. 2005;14(3):151-4.
16. Török ME, Nghia HD, Chau TT, et al. Validation of a diagnostic algorithm for adult tuberculous meningitis. *Am J Trop Med Hyg*. 2007;77(3):555-9.
17. British Medical Research Council, Streptomycin treatment of tuberculous meningitis. *Br Med J*. 1948:582–97.
18. van Toorn R, Springer P, Laubscher JA, et al. Value of different staging systems for predicting neurological outcome in childhood tuberculous meningitis. *Int J Tuberc Lung Dis* 2012;16(5):628-32.
19. Andronikou S, Smith B, Hatherhill M, et al: Definitive neuroradiological diagnostic features of tuberculous meningitis in children. *Pediatr Radiol* 2004;34(11):876-85.