Improving early diagnosis of tuberculous meningitis in children

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3.2 Diagnostic accuracy of a uniform tuberculous meningitis research case definition in children

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ABSTRACT

BACKGROUND: Bacteriological confirmation of tuberculous meningitis (TBM) is problematic and rarely guides clinical management. A uniform TBM case-definition has been proposed for research purposes, but its diagnostic accuracy in a clinical setting has not been evaluated.

METHODS: We prospectively enrolled patients with meningitis confirmed by cerebrospinal fluid analysis aged 3 months to 13 years at Tygerberg Children's Hospital, Cape Town, South Africa. Participants were investigated for TBM, bacterial and viral meningitis. Criteria that differentiated TBM from other causes were explored and the accuracy of a probable TBM score assessed by comparing bacteriologically-confirmed cases to "non-TBM" controls.

RESULTS: Of 139 meningitis suspects, 79 were diagnosed with TBM (35 bacteriologically-confirmed), 10 with bacterial meningitis and 50 with viral meningitis. Among bacteriologically-confirmed TBM, 15 were *M. tuberculosis* culture positive, 20 were culture negative but positive on GenoType MTBDR*plus*® and Xpert MTB/RIF®, 18 were positive on only a single commercial nucleic acid amplification test. A probable TBM score provided good diagnostic accuracy; sensitivity 74% (95% confidence interval (57-88%) and specificity 97% (95% confidence interval 86-99%) compared to bacteriologically-confirmed TBM.

CONCLUSION: A probable TBM score demonstrated excellent specificity compared to bacteriological confirmation, justifying consideration as a "rule-in" test. However, accurate diagnosis of early TBM remains a challenge.

INTRODUCTION

In 2013, there was an estimated 9.0 million new tuberculosis (TB) cases world-wide.[1] Central nervous system involvement, mostly tuberculous meningitis (TBM), is considered to account for approximately 1% of all cases.[2] Although TB is predominantly a pulmonary disease, extrapulmonary involvement is particularly common in young children and immune-compromised individuals.[3] In TB endemic areas with access to routine *Haemophilus influenza* type-B and pneumococcal vaccination, such as Cape Town (South Africa), TBM has surpassed other causes of bacterial meningitis.[4] In clinical practice, diagnosis is based on a combination of clinical, laboratory, and neuroimaging findings.

The early clinical presentation of TBM is often non-specific. With delayed treatment initiation TBM outcome is often poor, emphasizing the importance of early and accurate diagnosis.[5,6] TBM is a paucibacillary disease and the sensitivity of cerebrospinal fluid (CSF) microscopy is low.[7] The sensitivity of CSF culture is increased compared to microscopy, but remains low and the result rarely influences clinical management due to delays of up to 6 weeks.[8-10] Nucleic-acid amplification tests (NAATs) offer the prospect of rapid and specific diagnosis, but sensitivity remains suboptimal. A recent meta-analysis assessing the accuracy of commercial NAATs for the diagnosis of TBM showed a sensitivity of 64% and specificity of 98%, compared to CSF culture.[11]

In clinical practice, TBM is diagnosed based on a combination of clinical, laboratory, and neuroimaging findings. Previous studies identified key characteristics suggestive of TBM. Initial symptoms and signs are non-specific but persistent, and include poor weight gain or weight loss, fever, and lethargy. More specific signs have a sub-acute onset and include meningeal irritation, reduced consciousness, focal neurological deficits, raised intracranial pressure, brainstem dysfunction, and cranial nerve palsies.[6] Typical CSF features include a moderately increased white cell count with lymphocyte predominance, increased protein, and decreased glucose. Apart from hyponatremia,[12] no peripheral blood test result has consistently been associated with TBM. On neuroimaging, hydrocephalus, basal ganglia infarctions, and basal meningeal enhancement are common features.[6]

Clinical prediction rules that differentiate TBM from other forms of meningitis in adults include five parameters: young age (<36 yrs), sub-acute presentation (symptom duration >5 days), normal peripheral white blood cell count, moderately raised CSF white cell count (<500 cells/ml), and lymphocyte predominance (CSF neutrophil proportion <50%).[13] Good diagnostic accuracy was obtained using both a composite clinical

case-definition and bacteriologically-confirmed TBM as reference standards,[14] but was reduced in human immunodeficiency virus (HIV)-infected patients.[15] Although macroscopically clear CSF with lymphocyte predominance may differentiate TBM from bacterial meningitis,[16] many additional characteristics (sub-acute onset, focal neurological deficit, low CSF/serum glucose ratio, and elevated CSF protein) were required to differentiate TBM from viral meningitis in adult patients.[17] Data that compare TBM to other causes of meningitis in children are limited.

The absence of standardized TBM diagnostic criteria hampers progress, since diagnostic accuracy measures are often reported against variable composite clinical reference standards. For this reason a uniform research case definition was proposed by an international panel of experts, categorizing patients as definite, probable, or possible TBM according to clinical, CSF, and neuroimaging findings (Table 1).[18] The diagnostic accuracy and potential clinical utility of the proposed case definition has not been prospectively evaluated. We aimed to describe the clinical features of children with suspected meningitis, identify criteria that differentiate bacteriologically-confirmed TBM from other forms of meningitis, and assess the diagnostic accuracy of the proposed TBM research case definition in clinical practice.

METHODOLOGY

This prospective study was conducted at Tygerberg Children's Hospital, a tertiary referral centre in Cape Town, South Africa. All children with meningitis confirmed by CSF analysis aged 3 months to 13 years were prospectively enrolled between January 2010 and June 2013.

Signs and symptoms

Patients underwent comprehensive clinical evaluation by a pediatric neurologist. A TB contact was determined as household contact within the previous 12 months with an adult receiving treatment for pulmonary TB. The following signs and symptoms were collected; fever (axillary temperature >38.5°C); seizures (generalized or partial); recent weight loss, or poor weight gain (documented in the Road to Health booklet); meningeal irritation; focal motor deficit (monoparesis, hemiparesis, quadriparesis); cranial nerve palsy (deficit in any of the cranial nerves, especially III and VI); extrapyramidal signs (dystonia and/or chorea, athetosis, ballismus); raised intracranial pressure (bulging fontanelle, setting sun sign, acute onset strabismus in infancy, papilledema in the older child).

Table 1. Diagnostic criteria in the uniform TBM research case definition[18]

	Diagnostic score
Clinical criteria (Maximum category score=6)	
Symptom duration of more than 5 days	4
Systemic symptoms suggestive of TB (1 or more of): weight loss/ (poor weight gain in children), night sweats or persistent cough > 2 weeks	2
History of recent close contact with an individual with pulmonary TB or a positive TST/IGRA in a child <10 years	2
Focal neurological deficit (excluding cranial nerve palsies)	1
Cranial nerve palsy	1
CSF criteria (Maximum category score=4)	
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 2.2mmol/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 X-ray suggestive of active TB (excluding miliary TB)	2
Chest X-ray suggestive of miliary TB	4
CT/ MRI/ US evidence for TB outside the central nervous system	2
AFB identified or *M.tuberculosis* cultured from another source i.e. lymph node, gastric washing, urine, blood culture	4
Exclusion of alternative diagnoses- An alternative diagnosis must be confirmed microbiologically, serologically or histopathologically	
Definite TBM = AFB seen on CSF microscopy, positive CSF *M.tuberculosis* culture, or positive CSF *M.tuberculosis* commercial NAAT in the setting of symptoms/signs suggestive of meningitis; or AFB seen in the context of histological changes consistent with TB brain or spinal cord together with suggestive symptoms/signs and CSF changes, or visible meningitis (on autopsy).	
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, 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, NAAT- nucleic acid amplification test

Clinical procedures

Routine special investigations included peripheral blood for full blood count and differential, renal function tests, liver transaminases, tuberculin skin testing, sputum or gastric washing microscopy and culture for *Mycobacterium tuberculosis* (*M.tuberculosis*), blood culture, and chest radiography. HIV screening included HIV enzyme-linked immunosorbent assay in children >18 months and <18 months without maternal HIV exposure (ARCHITECT® HIV Ag/Ab Combo; Abbott Laboratories, Abbott Park, IL, USA). HIV DNA polymerase chain reaction (PCR) was performed in children <18 months exposed to maternal HIV or where the HIV enzyme-linked immunosorbent assay screening test was positive (Roche CAP/CTM HIV-1 assay; Roche Molecular Systems, Branchburg, NJ, USA). Neuroimaging, including brain computed tomography (CT), and magnetic resonance imaging, was performed if clinically indicated (routine in TBM, but not in uncomplicated viral and bacterial meningitis).

CSF, by lumbar puncture, was evaluated in all patients including macroscopic appearance, total and differential cell count, protein, glucose, chloride, Gram stain, India ink examination, auramine "O" fluorescence microscopy, culture for pyogenic bacteria, culture for *M.tuberculosis*, GenoType MTBDR*plus*® and GeneXpert MTB/RIF® assays. When viral meningitis was suspected, a CSF PCR panel for cytomegalovirus, Epstein-Barr virus, enteroviruses, human herpesvirus-6, herpes simplex 1 & 2 and varicella zoster was performed.

For *M.tuberculosis* culture, 0.5 ml of CSF was directly inoculated into a Mycobateria Growth Indicator Tube (MGIT; Becton Dickinson, Sparks, MD, USA) and incubated at 37°C. The presence of acid-fast bacilli was verified by Ziehl-Neelsen staining and microscopy. The Genotype MTBDR*plus*® assay analyzed a CSF volume of 0.5ml, with a 160 colony forming unit/ml limit of detection. Improvements in the DNA extraction from sonication and heat (version 1) to a chemical method (version 2), enabled its usage on smear microscopy-positive and -negative samples. For the *Xpert MTB/RIF*® assay, an aliquot of 1 ml CSF was mixed with 2 ml Xpert Sample Reagent (Cepheid) and incubated at 37°C. All further processing happened automatically (GeneXpert Dx 4.0, Cepheid). Bacterial load was semi-quantitatively reported, with rifampicin resistance indicated separately. The limit of detection was 100 colony forming units/ml.

Descriptive case definitions

For descriptive purposes children were categorized as TBM and non-TBM. TBM was clinically diagnosed when CSF changes were suggestive of TBM (clear appearance and pleocytosis 10-500/µl and/or increased protein >1g/dl, and/or decreased glucose defined as <2.2mmol/l or CSF to serum ratio of <50%) and at least two of the follow-

ing criteria were met: 1) recent contact with an infectious TB source case or a positive tuberculin skin test, 2) a chest x-ray suggestive of TB, 3) CT or magnetic resonance imaging demonstrating features of TBM (hydrocephalus, meningovascular enhancement, infarction, and/or granuloma/s).[19] TBM was staged according to revised British Medical Research Council criteria as: 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 and Stage III) GCS <11.[20,21]

Non-TBM included bacterial and viral meningitis. Bacterial meningitis was identified by either 1) microscopy and/or culture confirmation of a bacterial pathogen on CSF or 2) culture confirmation of a bacterial pathogen on blood and purulent CSF.[22] Viral meningitis was diagnosed when a viral pathogen was identified by CSF PCR, or the clinical outcome was favourable with only supportive care and other causes of meningitis excluded.[17]

Comparative case definitions

For comparative purposes, children with bacteriologically-confirmed (definite) TBM were used as the reference standard. "Definite TBM" included meningitis suspects with acid-fast bacilli seen on CSF microscopy, positive CSF *M.tuberculosis* culture and/or detection by commercial NAAT. "Definite TBM" cases were differentiated into probable and possible TBM cases (not taking into account bacteriological confirmation) in order to evaluate the proposed research case definition criteria,[18] with points allocated for 1) clinical presentation, 2) CSF findings, 3) neuroimaging, 4) evidence of extraneural TB and 5) additional laboratory criteria (Table 1). "Probable TBM" required a score >9 if neuroimaging was not performed and >11 if neuroimaging was performed, while "possible TBM" required a score 6-9 if neuroimaging was not performed and 6-11 if neuroimaging was performed.

STATISTICAL ANALYSIS

Data analysis was performed using Statistical Package for the Social Sciences version 21 (SPSS Inc, Chicago, IL, USA). For descriptive purposes, frequencies were determined for categorical variables, with median and interquartile range reflected for continuous variables. The X^2 and Fisher's exact tests were used to assess differences between continuous and categorical variables respectively. The level of significance was set at $p < 0.05$ (2-sided). For diagnostic accuracy assessment a multivariable logistic regression model was constructed to identify criteria that were independently associated with bacteriologically-confirmed TBM, compared to "non-TBM". Three

criteria that were identified by both forward and backward stepwise selection at the 15% level were then used to construct a receiver operating characteristic curve. The diagnostic accuracy between the multivariable model and a probable TBM score using criteria from the proposed uniform research case definition was compared.

The study was approved by the Human Research Ethics Committee of Stellenbosch University, South Africa (study nr. N11/01/006).

RESULTS

We identified 139 children with suspected meningitis: 79 were bacteriologically or clinically diagnosed with TBM, 10 with bacterial meningitis and 50 with viral meningitis.

Table 2 reflects the relevant demographic and clinical characteristics. Few TBM patients presented with early (stage I) disease; 85% had stage II or III disease. Four bacterial meningitis cases had positive CSF cultures; 2 *Streptococcus pneumoniae* and 2 *Neisseria meningitides*. Twenty children with viral meningitis had viral pathogens detected by PCR in their CSF, including cytomegalovirus (3), Epstein-Barr virus (2), herpes simplex type-2 virus (1), human herpes virus-6 (2) and human enterovirus (12). Among those clinically diagnosed with TBM, 35/79 (44%) had bacteriological confirmation; 3/35 (9%) by microscopy, 15/35 (43%) by culture, and 29/35 (83%) by commercial NAAT.

Table 3 shows the bacteriological yield achieved with various methods. Among commercial NAATs, the sensitivity of GenoType MTBDR*plus*® was (20/35; 57%) and Xpert MTB/RIF® (14/35; 40%). With one exception, all cases with a positive

Table 2. Demographics, symptoms and signs in children with TB, bacterial and viral meningitis

	TB meningitis*	Bacterial meningitis	Viral meningitis
DEMOGRAPHICS			
		Median (IQR)	
Age (in months)	31 (21-54)	29 (20-81)	62 (22-92)
Monthly income (US $)	150 (50-250)	120 (28-200)	173 (73-300)
		n (%)	
Gender (male)	41 (52)	5 (50)	38 (76)
Informal housing	29 (37)	3 (30)	13 (26)
Clinic visits	2 (2-3)	2 (2-3)	2 (2-3)
TB contact	30 (38)	4 (40)	23 (46)

Table 2 (continued)

	TB meningitis*	Bacterial meningitis	Viral meningitis
SYMPTOMS			
Fever	62 (79)	9 (90)	44 (88)
Vomiting	51 (65)	7 (70)	35 (70)
Seizures	24 (30)	2 (20)	7 (14)
Weight loss	20 (25)	1 (10)	10 (20)
Coughing	26 (33)	4 (40)	14 (28)
Poor feeding	49 (62)	5 (50)	27 (54)
Headache	27 (34)	3 (30)	32 (64)
>5 days duration	45 (57)	3 (30)	10 (20)
SIGNS			
GCS <11	27 (34)	4 (40)	4 (8)
11-14	31 (39)	3 (30)	1 (2)
Normal	21 (27)	3 (30)	45 (90)
Meningism	22 (28)	4 (40)	19 (38)
Focal motor deficit	28 (35)	3 (30)	0 (0)
Cranial nerve palsy	25 (32)	1 (10)	0 (0)
Extrapyramidal signs	6 (8)	0 (0)	0 (0)
Raised ICP	11 (14)	3 (30)	3 (6)
Brainstem dysfunction	9 (11)	2 (20)	2 (4)
TOTAL	**79**	**10**	**50**

*As per descriptive case definition defined in methods; 15% TBM stage I, 15% stage IIa, 35% stage IIb, 35% stage III
TB – tuberculosis; GCS – Glasgow Coma Scale; ICP – intracranial pressure

NAAT test on CSF had clinical and radiological signs suggestive of TBM. A single case diagnosed as stage I TBM on account of a positive GenoType MTBDR, presented with non-specific symptoms and CSF pleocytosis but had no other clinical, CSF, or imaging findings typical of TBM. Of the 29 cases diagnosed by NAAT, 21 only tested

Table 3. Overview of bacteriological confirmation achieved in 35 children with "definite" TB meningitis.

Bacteriological confirmation from CSF	Smear microscopy	MGIT® culture	Xpert MTB/RIF®	GenoType MTBDR*plus*®
Smear microscopy	**3** (0)*	2	0	1
MGIT® culture	2	**15** (1)*	5	7
Xpert MTB/RIF®	0	5	**14** (4)*	5
GenoType MTBDR*plus*®	1	7	5	**20** (7)*

CSF- cerebrospinal fluid
*The number in brackets reflects the patients who tested positive with a particular method only

positive for one of the two NAAT tests used in this study. CSF volume recorded in 52 patients (42 TBM and 10 non-TBM) was relatively small (mean 2.1ml: range 0.5 ml to 5.0 ml), with no clear correlation between CSF volume and diagnostic yield.

Table 4 summarizes laboratory and radiological features of children diagnosed with TBM compared to those diagnosed with bacterial and viral meningitis. Overall the

Table 4. Special investigations and imaging findings in children with TB, bacterial and viral meningitis

	Bacteriologically confirmed TBM	Not bacteriologically confirmed TBM	Bacterial meningitis	Viral meningitis
		n (%)		
HIV-infected	3 (9)	3 (7)	2 (20)	2 (4)
TST ≥10mm	7 (20)	14 (32)	0 (0)	3 (6)
Hyponatremia*	12 (34)	12 (27)	1 (10)	4 (8)
CSF				
		n (%)		
Clear	33 (94)	38 (86)	6 (60)	45 (90)
Leucocytes 10-500 cells/L	28 (80)	32 (73)	8 (80)	42 (84)
Lymphocytes > 50%	31 (89)	37 (84)	6 (60)	34 (68)
Protein >1g/L	24 (69)	24 (55)	5 (50)	7 (14)
Glucose <2.2mmol/L	16 (46)	19 (43)	6 (60)	5 (10)
		Median (IQR)		
Leucocytes (cells/uL)	129 (63-268)	36 (11-133)	279 (72-558)	70 (36-174)
Neutrophils (cells/uL)	12 (4-31)	1 (0-7)	46 (6-369)	11 (0-54)
Lymphocytes (cells/uL)	122 (50-215)	35 (9-114)	127 (28-401)	40 (23-134)
Protein (g/L)	1.9 (1.0-2.0)	1.2 (0.8-2.0)	1.6 (0.8-2.2)	0.4 (0.2-0.8)
BRAIN CT				
		n (%)		
Precontrast basal hyperdensity	5 (14)	10 (23)	1 (10)	0 (0)
Hydrocephalus	24 (69)	38 (86)	4 (40)	1 (2)
Infarctions	4 (11)	18 (41)	1 (10)	1 (2)
Basal meningeal enhancement	24 (69)	35 (80)	3 (30)	2 (4)
Tuberculoma(s)	5 (14)	9 (20)	0 (0)	0 (0)
Extraneural TB				
CXR suggestive of TB	14 (40)	19 (43)	1 (10)	7 (14)
***M.tuberculosis* isolated**	11 (31)	11 (25)	0 (0)	1 (2)
TOTAL	**35**	**44**	**10**	**50**

* Serum sodium <130mmol/L

TBM – tuberculous meningitis; TST- tuberculin skin test; CSF- cerebrospinal fluid; CT- computed tomography

proportion of HIV-infected children was low (9%) and not increased among TBM cases. The vast majority of TBM patients had neuroimaging abnormalities with hydrocephalus and basal meningeal enhancement the most common findings.

Table 5 includes uni- and multivariate analyses assessing the diagnostic value of various clinical, laboratory and CT criteria in TBM and non-TBM cases; the multivariable

Table 5. Analysis of clinical, laboratory and radiological criteria in children with bacteriologically-confirmed TB meningitis compared to "non-TB meningitis"

Criteria	OR (95% CI)	p value
HIV-infected	1.08 (0.27-5.15)	0.93
Sub-acute onset	3.10 (1.27-7.58)	0.01
Seizures	2.27 (0.82-6.29)	0.11
Weight loss	1.54 (0.57-4.20)	0.40
TB contact	0.82 (0.35-1.90)	0.64
GCS <15	6.77 (2.66-17.21)	<0.01
Focal deficit	6.58 (1.64-26.31)	<0.01
Cranial nerve palsy	23.60 (2.87-194.30)	<0.01
Raised ICP	1.50 (0.42-5.33)	0.53
TST ≥10mm	4.75 (1.14-19.77)	0.02
Serum Na <130mmol/L	4.66 (1.41-15.41)	<0.01
CSF clear	2.91 (0.59-14.33)	0.17
CSF 10-500 cells/uL	0.80 (0.27-2.34)	0.68
CSF lymphocytes >50%	3.88 (1.20-12.50)	0.02
CSF protein >1g/L	10.22 (3.78-27.66)	<0.01
CSF glucose <2.2mmol/L	4.99 (1.89-13.18)	<0.01
CT hydrocephalus	7.86 (2.32-26.63)	<0.01
CT infarctions	1.36 (0.23-8.08)	0.74
CT basal meningeal enhancement	7.86 (2.32-26.63)	<0.01
CT tuberculoma(s)	*0 non-TBM pts	0.06
Chest X-ray suggestive of TB	2.33 (0.81-6.75)	0.11
***M.tuberculosis* from extraneural source**	9.43 (1.06-84.04)	0.02
Criteria that differentiated TBM from non-TBM on multivariable analysis*		
Cranial nerve palsy	9.94 (0.89-110.86)	0.06
CSF protein >1g/L	11.55 (3.72-35.87)	<0.01
TST ≥10mm	3.89 (0.65-23.33)	0.14

OR - odds ratio, CI - confidence interval; TST - tuberculin skin test; GCS - Glasgow Coma Scale; ICP - intracranial pressure, CSF - cerebrospinal fluid; CT – computed tomography; TB – tuberculosis; OR-odds ratio; CI - confidence interval

*Neuro-imaging criteria had to be excluded since these were performed on a minority of non-TBM patients

logistic regression analysis excluded neuroimaging findings, since this was performed in a minority (62/157; 39%) of non-TBM cases. Three variables were significantly associated with TBM on multivariable analysis; cranial nerve palsy, TST ≥10mm and CSF protein >1g/L. However these three criteria had sensitivity of only 0.50, 95% confidence interval (CI) 0.12-0.88, in stage I disease compared to 0.88 (95% CI 0.70-0.98) in stage II and II disease. A receiver operating characteristic curve using the three-variable predictive model delivered an area under the curve of 0.82 (95% CI 0.73-0.92); sensitivity 0.79 (95% CI 0.61-0.91) and specificity 0.78 (95% CI 0.65-0.88) (Figure 1).

Of 79 children clinically diagnosed with TBM, 66 scored as "probable TBM", 12 as "possible TBM", and one as "not TBM" using the proposed research case definitions. Using clinically diagnosed TBM cases as the reference standard, a probable TBM score had sensitivity of 0.84 (95% CI 0.74-0.91) and specificity of 0.95 (95% CI 0.86-0.99). The ability to detect stage I TBM was sub-optimal with a sensitivity of only 42% (5/12). Among 35 bacteriologically-confirmed TBM cases ("definite TBM"), 26 had a probable TBM score; sensitivity 0.74 (95% CI 0.57-0.88) and specificity 0.95 (95% CI 0.86-0.99). A possible TBM score had greater sensitivity 0.97 (95% CI 0.85-1.00), but reduced specificity 0.48 (95% CI 0.35-0.62).

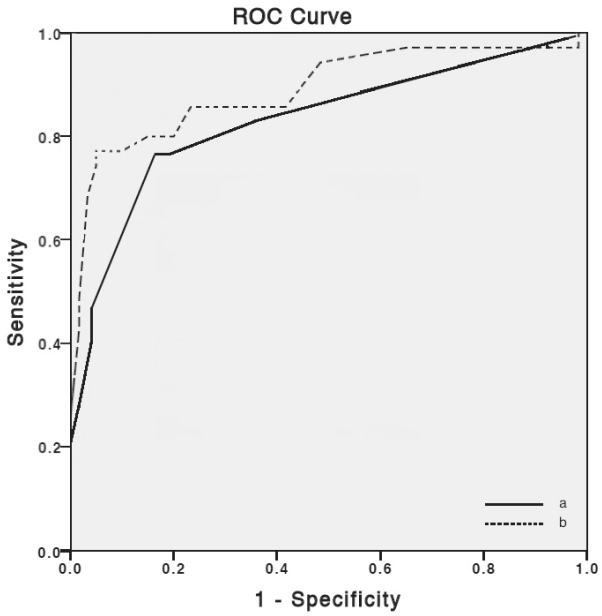

Figure 1. ROC curves of a) a "probable TBM" score and b) the three criteria identified on multivariable analysis*; using bacteriologically-confirmed TBM" as the reference standard
*Cranial nerve palsy, elevated CSF protein and a TST ≥10mm (Table 5)

DISCUSSION

This study represents the first prospective evaluation of the diagnostic accuracy of the recently proposed uniform TBM research case definition. A probable TBM score demonstrated reasonable sensitivity, 84% in clinically diagnosed and 74% in bacteriologically-confirmed TBM cases, with excellent specificity. The clinical importance of a reliable clinical case definition for TBM is emphasized by the fact that bacteriological confirmation was achieved in less than half (44%) of the children clinically diagnosed with TBM, despite exhaustive evaluation. The high specificity of a probable TBM score justifies its use as an alternative reference standard to bacteriological confirmation in future studies, although the diagnosis and study inclusion of early stage 1 disease remains problematic.

The low incidence of stage I TBM in our study is consistent with other studies from TB endemic areas and underlines the difficulty in diagnosing TBM early.[6,23] The poor sensitivity of a probable TBM score to diagnose stage I TBM versus stage II and II TBM was disappointing but not unexpected, since scoring is based on clinical, CSF and radiological findings which all tend to become more pronounced as the disease progresses. The diagnosis of early stage I TBM remains a major clinical dilemma. Since the early presentation of TBM is so non-specific, diagnosis is essentially reliant on a very high clinical index of suspicion in vulnerable young children with recent TB exposure and persistent non-specific signs despite treatment for other possible causes. Early diagnosis and treatment of TBM is vital to ensure an optimal outcome and this poses a major clinical dilemma.[6,23]

The majority of CSF specimens tested positive by means of a single bacteriological-confirmation method, highlighting the need for multiple diagnostic tests in children suspected with TBM and optimizing bacteriological confirmation in paucibacillary CSF specimens; especially with the collection of low CSF volumes. It has been suggested that high volumes of CSF should be collected and concentrated to improve diagnostic yields, as well as provide complete drug susceptibility information.[24,25] The relatively low CSF volumes collected in this study prevented specimen concentration, however, the volumes obtained are consistent with what is achieved in routine pediatric practice. The GenoType MTBDR*plus*® assay was found to be the most sensitive single test. There are concerns about the possibility of cross-contamination with the GenoType MTBDR*plus*® assay, but this was not a major concern in the current study; 19/20 patients had multiple clinical-radiological signs consistent with TBM and a single one had CSF pleocytosis only.

A reliable clinical reference standard should be more representative of the disease spectrum seen in clinical practice and be more feasible than bacteriological confirmation in TB endemic areas. The overall performance of a probable TBM score was better than the three-variable predictive model, but the use of three simple criteria (cranial nerve palsy, TST ≥10mm and elevated CSF protein) may offer better clinical utility in areas with limited access to neuro-imaging. However, its diagnostic accuracy is likely to have been over-estimated, given that the analysis was optimized for the study cohort and the non-TBM arm included relatively few children with bacterial, fungal or complicated viral meningitis.

A number of clinical prediction rules to differentiate TBM from bacterial meningitis in adults from resource-poor settings have been proposed.[13,14,16] However, most of these were based on case-control studies and failed to include all meningitis suspects. Our study focused on a pediatric population and is strengthened by the inclusion of bacterial and viral meningitis, as encountered in every-day clinical practice. We were unable to determine the role of HIV co-infection, because of the relatively low prevalence of HIV co-infection among TBM patients in our cohort (8%). Karande et al. also found that only 6.5% of 123 children with clinically diagnosed TBM had HIV co-infection.[26] TBM seems to be proportionally less common than other TB manifestations among HIV-infected children; an intriguing finding which may reflect the contribution of an appropriate immune response to TBM pathology.[27] Immune reconstitution inflammatory syndrome, a well-recognized complication in HIV-infected patients with TBM who are initiated on antiretroviral therapy provides further support for the role of immunity in the pathogenesis of TBM.[28-30]

Our study is limited by the fact that the study cohort included few cases of bacterial meningitis. *Haemophilus influenza* type-B and pneumococcal vaccination are provided free of cost to all children in South Africa. Neuroimaging was performed in a minority of non-TBM cases, which prevented its inclusion in multivariable analysis. However, neuroimaging is not routinely performed in non-TBM suspects and ethical justification would have been problematic. The relatively low proportion of bacteriologically-confirmed TBM cases reflects the paucibacillary nature of the disease, sub-optimal sensitivity of available diagnostic tests, and low CSF volumes obtained.[5,8-11] The study was performed at a single hospital which may limit generalization of the study findings to other settings, but Tygerberg Children's Hospital serves a population that share a similar disease burden and health challenges experienced in other TB endemic areas.

In conclusion, a probable TBM score demonstrated good diagnostic accuracy in this prospective study,[18] both in children with clinically diagnosed and bacteriologically-confirmed TBM. The excellent specificity achieved support its use as an alternative reference standard in research studies, at least in settings with a similar disease spectrum among non-TBM patients, although its clinical utility is limited in resource-limited settings.

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CONFLICT OF INTEREST

None of the authors had to declare a conflict of interest.

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