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**Rapid Accurate Identification of Tuberculous Meningitis Among South African Children
Using a Novel Clinical Decision Tool**

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Abbreviated Title: Rapid Clinical Decision Tool to Diagnose Childhood TB Meningitis

Running Head: Rapid Diagnosis of Childhood TB Meningitis

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ABSTRACT

Introduction: Early diagnosis of tuberculous meningitis (TBM) is crucial to achieve optimum outcomes. There is no effective rapid diagnostic test for use in children. We aimed to develop a clinical decision tool to facilitate the early diagnosis of childhood TBM.

Methods: Retrospective case control study across 7 hospitals in KwaZulu-Natal, South Africa (2010-2014). We identified the variables most predictive of microbiologically confirmed TBM in children (3 months-15 years) by univariate analysis. These variables were modelled into a clinical decision tool and performance tested on an independent sample group.

Results: Of 865 children with suspected TBM, 3% (25) were identified with microbiologically confirmed TBM. Clinical information was retrieved for 22 microbiologically confirmed cases of TBM and compared with 66 controls matched for age, ethnicity, sex and geographical origin. The 9 most predictive variables among the confirmed cases were used to develop a clinical decision tool (CHILD TB LP): altered Consciousness; caregiver HIV infected; Illness length >7 days; Lethargy; focal neurological Deficit; failure to Thrive; Blood/serum sodium <132mmol/L; CSF >10 Lymphocytes $\times 10^6/L$; CSF Protein >0.65g/L. This tool successfully classified an independent sample of 7 cases and 21 controls with a sensitivity of 100% and specificity of 90%.

Conclusion: The CHILD TB LP decision tool accurately classified microbiologically confirmed TBM. We propose that CHILD TB LP is prospectively evaluated as a novel rapid diagnostic tool for use in the initial evaluation of children with suspected neurological infection presenting to hospitals in similar settings.

Key Words: Tuberculous meningitis; children; diagnosis; case definition; scoring systems

INTRODUCTION

Tuberculous meningitis (TBM) is a devastating illness that disproportionately affects young children.¹⁻³ It is the most common cause of meningitis affecting children in South Africa.⁴ Approximately 50% of cases result in death or disability.^{1-3,5,6} The early diagnosis and treatment of TBM is important to ensure optimum outcomes.^{2,5-7} Its non-specific clinical presentation means that treatment is often only initiated after irreversible damage has occurred.^{2,6,8} The current standard diagnostic test is cerebrospinal fluid (CSF) culture which can take weeks, and has been reported with varying degrees of sensitivity.⁹⁻¹¹ The use of Xpert MTB/RIF (Cepheid, Sunnyvale, California) on CSF samples offers a more rapid diagnosis of TBM, but it has also been reported to have variable sensitivity.¹² Only 4 of 22 high-burden developing countries have recommended the use of Xpert MTB/RIF on CSF samples largely due to resource constraints.¹³ Several studies have proposed clinical decision tools that facilitate the early diagnosis of TBM in adults, but few studies have reported individual clinical variables that are predictive of TBM in children.^{3,7,14,15} The utility of adult decision tools in pediatric clinical presentations is limited because of the inclusion of variables such as headache, which are difficult to assess in infants and young children.¹⁶ We set out to develop a rapid clinical decision tool based on the most commonly recorded and predictive markers of childhood TBM. Predictive variables were identified using information collected retrospectively from clinical records from a cohort of children with suspected TBM presenting to hospitals in KwaZulu-Natal (KZN), the province of South Africa most heavily burdened by TB with an incidence of 922 cases per 100,000 in 2013.¹⁷ Predictive variables were modelled into a rapid clinical decision tool, which we propose for use in the initial evaluation of children with suspected central nervous system (CNS) infection presenting to hospitals in similar settings.

METHODS

A retrospective case-control study was performed across the 7 hospitals with the highest number of microbiologically proven childhood TBM cases in KZN: Addington Hospital, Edendale Hospital, Inkosi Albert Luthuli Central Hospital, Grey's Hospital, King Edward VIII Hospital, RK Khan Hospital and Mahatma Gandhi Memorial Hospital. Children with suspected TBM were defined as having had CSF sent to the laboratory for *Mycobacterium tuberculosis* (Mtb) detection by microscopy and culture. Children (3 months to 15 years) with suspected TBM who presented to these hospitals from June 2010 to January 2014 inclusive were identified from the National Health Laboratory Service computerized records. Candidate clinical variables potentially predictive of TBM were identified from the published literature and included in a case report form (Fig., Supplemental Digital Content 1, <http://links.lww.com/INF/C807>).^{3,7,14,15,18} The case report forms were then completed using clinical information retrieved from the case notes of the identified children. Cases were defined as children with microbiologically confirmed TBM by CSF culture. The use of Xpert MTB/RIF on CSF samples had not been implemented in KZN during our study period. Controls were defined as children with suspected TBM, who were unlikely to have had TBM: Mtb not detected in the CSF by microscopy and culture; did not receive anti-tuberculous treatment; and did not have a poor outcome (no death or neurologic sequelae), *or* another CNS pathogen was isolated. Cases were matched with three controls for age, sex, ethnicity and geographical origin to maximize the power of the study.¹⁹ Cases and controls were randomly allocated into development (67% of patients) and test groups (33% of patients). The development group was used to identify the variables (with less than 20% missing data) that were most significantly predictive of TBM by univariate analysis. Analyses were performed using SPSS (Version 20.0.0.1, IBM Corporation). The significance level was set

at 5%. Continuous variables were dichotomized using Receiver Operator Characteristic (ROC) analyses to yield threshold values of maximum significance. Univariate and multivariate logistic regression were used to identify the most appropriate variables and the most efficient model. The decision tool was created using the most clinically independent variables from those identified in the univariate analysis. The most sensitive diagnostic threshold value for the tool was identified by ROC analysis, without compromising on specificity. Finally, the performance of the decision tool was evaluated on the test group of cases and controls.

All personal information regarding study participants was treated confidentially. The study received ethical approval from the Department of Health, KwaZulu-Natal (reference HRKM323/13), University of KwaZulu-Natal (reference BE334/13) and University of Liverpool (reference RETH000667).

RESULTS

During the study period 865 children met inclusion criteria for suspected TBM (Fig., Supplemental Digital Content 2, <http://links.lww.com/INF/C808>). TBM was microbiologically confirmed by CSF culture in 3% (25/865). One case (1/25) was also identified by detection of acid-fast bacilli during CSF microscopy. No cases were detected by Xpert MTB/RIF which was not used in KZN during the study period. A CNS infection other than TBM was confirmed by culture and/or polymerase chain reaction in 6% (55/865). Clinical case notes were retrieved for 88% (22/25) of the children with microbiologically confirmed TBM. Drug susceptibility testing revealed multi-drug resistant (MDR) Mtb in 23% (5/22) and extremely-drug resistant (XDR) Mtb in 9% (2/22). The baseline characteristics, diagnosis and outcome of the 22 cases and 66 matched controls are displayed in Table 1. The median age of cases was 5.2 years (range: 5 months -13.3 years) and matched controls was 4.7 years (range: 4 months - 13.2 years). There

were no significant differences between cases and matched controls with regards to age, sex, ethnicity, geographical origin, HIV status and whether a chest x-ray or extraneural imaging was performed. Cases were significantly more likely to have had neuroimaging performed than controls ($p<0.001$). The matched controls contained 6% (4/66) with a CNS infection other than TBM, and in the rest no pathogen was isolated. Outcome was significantly poorer in terms of morbidity for cases than controls ($p<0.001$), though there was no significant difference in survival ($p=0.06$). Four cases who left hospital without a diagnosis were later confirmed to have TBM. Outcome data was available for two of these cases: both re-presented to hospital, were commenced on anti-tuberculous treatment and had severe neurological sequelae.

Children were randomly allocated into a 'development' (15 cases and 45 controls) or 'test' group (7 cases and 21 controls). The development group was used to identify variables predictive of TBM. Univariate analyses identified the variables that differed significantly between cases and controls (Table 2). Continuous variables were transformed to dichotomous variables using ROC threshold values of maximum significance e.g. serum sodium $\leq 132\text{mmol/L}$ and CSF protein $\geq 0.65\text{g/L}$ were found to be more predictive than standard laboratory reference ranges that define decreased serum sodium or raised CSF protein. Variables that were not significantly predictive of TBM included: seizures, fever; vomiting; persistent cough for more than 2 weeks; regular/close contact with someone with TB within last year; weight-for-age centile; irritability; neck stiffness; bulging fontanelle; HIV status; WHO HIV Clinical Stage; use of antiretroviral treatment (ART); time since initiation of ART; hemoglobin; peripheral white cell count; serum creatinine; CSF appearance; CSF polymorphonuclear cell count; and CSF erythrocyte count. Variables for which there were greater than 20% missing data were excluded: headache; photophobia; night sweats; Glasgow Coma Scale; papilledema; Mantoux result; serum glucose

(thus CSF: serum glucose ratio); CSF opening pressure; chest x-ray; computed tomography (CT) head; extraneural imaging; and extraneural Mtb detection.

The clinical decision tool was modelled from the most independently predictive variables from Table 2. Backward regression identified co-dependent parameters. We retained the most significant parameters based on univariate analysis. Weighting variables based on their odds ratio in discriminating between cases and controls did not provide additional benefit to the model. Furthermore, ROC analysis identified that giving individual weightings for presence of abnormal posture, abnormal reflexes, increased tone and cranial nerve palsy, performed no better than asking whether ‘any new focal deficit’ was present. Similarly CSF lymphocytes and CSF protein were used in place of CSF white cell count, CSF glucose and CSF chloride. ‘Abnormal behavior’ was also discarded as it did not provide any additional value to the new models. There was insufficient data to include several variables previously recognized to add specificity to the diagnosis of TB (e.g. Mantoux, chest x-ray, extraneural Mtb detection and neuroimaging). The decision tool was summarized by the acronym ‘CHILD TB LP’ (Figure 1). A cut-off score of ≥ 4 out of 9 gave optimum sensitivity (93%) and specificity (89%) on ROC analysis of the development group. Finally, the CHILD TB LP tool was assessed on the test group, in whom there was missing data for a median of 1 (range 0-4) out of 9 variables. The CHILD TB LP tool performed with 100% sensitivity, 90% specificity and 93% accuracy in the test group.

DISCUSSION

We developed a rapid clinical decision tool to facilitate the accurate early diagnosis of TBM in children before CSF Mtb culture results become available. In keeping with previous studies, our data indicate a timely diagnosis of TBM is not always achieved through conventional diagnostic

approaches, with 4 out of 22 children with culture proven TBM discharged from hospital without anti-tuberculous treatment before their diagnoses were confirmed.^{2,3,6,7}

The CHILD TB LP decision tool is comprised of the most predictive, independent, highly documented and locally relevant variables. The tool's variables can be ascertained by history-taking or simple bedside clinical examination. It does not rely on tests that are not universally available across KZN such as neuroimaging or TB culture, which if depended upon can introduce unacceptable delays in the diagnosis and treatment of TBM.²⁰ To our knowledge, there is only one previous study that developed a clinical decision tool to facilitate diagnosis of childhood TBM based on primary clinical data.¹⁵ The tool includes similar variables to CHILD TB LP such as illness length >7 days and any focal deficit. However this previous tool is arguably limited by the need to assess patients for optic atrophy, given the specialist training required to perform fundoscopy accurately.²¹

Neuroimaging is not required to make a diagnosis of TBM using our tool. Nevertheless, the value of neuroimaging to detect intra-cranial complications (such as tuberculomas and hydrocephalus) and to guide neurosurgical intervention among suspected TBM patients compelled us to include a prompt to perform neuroimaging in suspected TBM patients within our tool.^{22,23}

Given the significant number of drug-resistant cases in our cohort, we also included a prompt to remind users of the importance of microbiological testing for TB in other samples (e.g. sputum). Structuring our variables into the acronym CHILD TB LP may improve adoption of the tool by clinicians, as the user-friendliness of a clinical decision tool has been shown to influence the success of its implementation.²⁴

Since the completion of our study, the use of Xpert MTB/RIF on extrapulmonary samples has been introduced across South African hospitals. The routine use of Xpert MTB/RIF has the potential to enable more rapid Mtb detection in CSF samples, and was recommended by the WHO in 2013.¹² However, a Ugandan study demonstrated that large volume (median: 6 mL, inter-quartile range: 4–10 mL) centrifuged CSF samples were required to achieve 72% sensitivity compared with a research case definition of TBM.²⁵ In practice, large CSF volumes are not always collected in children or infants, in part, because of concerns around safety.²⁶ Furthermore, a meta-analysis of Xpert MTB/RIF in CSF samples demonstrated a pooled sensitivity of 79.5% (95% confidence interval: 62.0%–90.2%) with culture as the reference standard.¹² Given the imperfect sensitivity of Xpert MTB/RIF and challenges surrounding sample collection, we would advocate our clinical decision tool should be assessed as an inexpensive adjunct to facilitate the accurate early diagnosis of TBM.

Apart from small sample size, a key limitation of our study is that our tool has been developed using retrospectively collected clinical data. We cannot confirm if the managing clinicians perceived the same level of risk of TBM among the cases and controls. This is potentially highlighted by significantly less neuroimaging undertaken in the control group. Furthermore, our study population was potentially limited by not including children who did not have CSF analysis for TB, but who may have been suffering from TBM. We also excluded children who were treated for TBM but did not have microbiologically confirmed TBM, to ensure that: i) cases were only children with a definite microbiological diagnosis of TBM; ii) controls were not biased by the potential confounder of having TBM that had not been microbiologically confirmed.

Despite the considerable level of irretrievable data for some variables, there were no systematic differences in missing data between cases and controls except neuroimaging. Dependent variables were excluded based on our subjective assessment of clinical correlation, and the resulting combinations of variables were modelled to produce a decision tool with maximum efficiency. Therefore, by including clinically independent variables and excluding variables with considerable missing data, we were able to focus our novel decision tool on the most highly documented and clinically available variables.

The rate of microbiologically confirmed CNS infections other than TBM was only 6% (55/865), which may reflect their low prevalence in our source population. However meningitis with CSF pleocytosis and no detectable pathogen was relatively more common among our control cohort (14%, 9/66), potentially reflecting culture-negative bacterial meningitis, particularly as local guidelines recommend empiric pre-hospitalization intramuscular ceftriaxone in suspected meningitis.²⁷

HIV-infection increases the risk of TBM and other forms of bacterial meningitis, but was not significantly predictive of TBM in our cohort, possibly reflecting the successful public sector rollout of ART across South Africa since 2004.²⁸⁻³⁰ In addition, our data did not demonstrate the previously reported predictive value of regular or close contact with a TB-infected adult. This may reflect poor knowledge or poor recall among historians or the successful implementation of household contact tracing and isoniazid preventative therapy.^{1,3,31} HIV-infected caregivers are commonly the household source of infection in childhood TB, and caregiver HIV status was significantly predictive of TBM in our cohort (independently of the child's HIV status).³² The inclusion of caregiver HIV status in our clinical decision tool might limit its applicability in settings of low HIV prevalence. HIV-exposed but uninfected children are at increased risk of

severe infection compared with HIV-unexposed children, possibly as a result of increased pathogen exposure, feeding practices, poor vertical antibody acquisition and impaired innate and T-cell immunity.³³⁻³⁵

We propose that the CHILD TB LP clinical decision tool is tested prospectively in children with suspected CNS infection presenting to hospitals in similar settings. Given Xpert MTB/RIF's relatively low sensitivity for Mtb in CSF (particularly in low volume samples), our clinical decision tool may still assist rapid diagnosis of TBM in settings where Xpert MTB/RIF is available.

CONFLICTS OF INTEREST AND SOURCES OF FUNDING

The authors declare no conflict of interest. Dr. Anu Goenka was supported by a Royal College of Physicians Thomas Watts Eden Fellowship. The study was supported by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Emerging and Zoonotic Infections at the University of Liverpool in partnership with Public Health England (PHE) and Liverpool School of Tropical Medicine (LSTM). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.

CONTRIBUTION STATEMENT

AG, BD, TS and MG conceived the study. AG, KM, KS, PJ, RS and BD collected the data. AV assisted with the statistical analysis. All authors contributed to the manuscript and read the final version. The authors would also like to acknowledge the help of the secretaries and clinical record clerks involved in the study, as well as the staff of the National Health Laboratory Service, in particular Ms. Nombali Makhoba and Dr. Amanda Khumalo.

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FIGURE LEGENDS

Figure 1. **A novel rapid clinical decision tool to identify TBM: CHILD TB LP**

SUPPLEMENTARY DIGITAL CONTENT

Figure, Supplementary Digital Content 1. **Case report form**

Figure, Supplementary Digital Content 2. **Selection of cases and matched controls**

ACCEPTED

Table 1. **Baseline characteristics, diagnosis and outcome**

Variable		Cases Confirmed TBM n=22	Controls Unlikely TBM n=66	Pearson Chi- Squared (df)	p-value
Age*	>3 months old to <1 year old	2 (9%)	6 (9%)	0.27 (2)	0.874
	>1 year old to <5 years old	8 (36%)	28 (42%)		
	>5 years old to <15 years old	12 (55%)	32 (49%)		
Sex*	Male	11 (50%)	33 (50%)	0.00 (1)	1.000
	Female	11 (50%)	33 (50%)		
Ethnicity*	Black	21 (95%)	63 (95%)	0.00 (1)	1.000
	Indian	1 (5%)	3 (5%)		
Geographical origin*	Durban area	17 (77%)	50 (76%)	0.02 (1)	0.885
	Pietermaritzburg area	5 (23%)	16 (24%)		
HIV status	Positive	11 (50%)	23 (35%)	2.37 (3)	0.500
	HIV exposed awaiting HIV test result	0	2 (3%)		
	Negative	9 (41%)	30 (45%)		
	Unknown	2 (9%)	11 (17%)		
Lumbar puncture	Performed	22 (100%)	66 (100%)	0.00 (1)	1.000
	Not Performed	0	0		
Neuroimaging	Performed	22 (100%)	25 (38%)	25.59 (1)	<0.001
	Not Performed	0	41 (62%)		
Chest X-Ray	Performed	13 (59%)	37 (56%)	3.27 (2)	0.195
	Not Performed	7 (32%)	28 (42%)		
	Not Recorded	2 (9%)	1 (2%)		
Extraneural imaging for TB	Performed	4 (18%)	6 (9%)	1.35 (1)	0.245
	Not Performed	18 (82%)	60 (91%)		
Final clinician diagnosis	TBM	18 (82%)	0	74.01 (13)	<0.001
	Viral infection	0	16 (24%)		
	Suspected or proven bacterial infection	1 (5%)	10 (15%)		
	Meningitis with CSF pleocytosis and no detectable pathogen	0	9 (13%)		
	Acute febrile encephalopathy of unknown cause	3 (13%)	4 (6%)		
	Febrile seizure	0	6 (9%)		
	Disseminated TB	0	5 (8%)		
	Pulmonary TB	0	5 (7%)		
	Pyogenic bacterial meningitis	0	4 (6%)†		
	Cerebral malaria	0	2 (3%)		
	Headache of unknown cause	0	2 (3%)		
	Guillain-Barré Syndrome	0	1 (2%)		
	Malignancy	0	1 (2%)		
	Stroke	0	1 (2%)		
Glasgow Outcome Score¹⁷ Very Poor Outcome		9 (41%)	3 (4%)	53.39 (3)	<0.001

(at discharge)		Poor Outcome	2 (9%)	1 (2%)		
		No-Mild Disability	2 (9%)	60 (91%)		
		Not Recorded	9 (41%)	2 (3%)		
Survival	Died		3 (14%)	2 (3%)	3.46 (1)	0.062
	Survived to Discharge		19 (86%)	64 (97%)		

*Baseline characteristic matched between cases and controls

† Comprising of: pneumococcal meningitis (3 cases), meningococcal meningitis (1 case)

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Table 2. **Univariate analysis of variables significantly predictive of TBM**

Variable	Cases Confirmed TBM n=15	Controls Unlikely TBM n=45	Odds Ratio* (95% confidence interval)	p-value	Missing Data† n=60
History of poor weight gain	10 (71%)	7 (16%)	13.2 (3.2-54.30)	<0.001	2 (3.3%)
Fatigue/reduced playfulness	11 (85%)	17 (41%)	7.8 (1.5-39.6)	0.010	6 (10.0%)
History of altered consciousness	12 (80%)	21 (47%)	4.5 (1.1-18.4)	0.036	0 (0%)
Caregiver HIV infected	10 (91%)	18 (47%)	11.1 (1.3-95.6)	0.014	11 (18.3%)
Abnormal behavior	6 (55%)	6 (13%)	7.8 (1.8-33.8)	0.008	4 (6.7%)
Any new focal deficit	11 (73%)	5 (11%)	22.0 (5.0-96.1)	<0.001	0 (0%)
Abnormal posture	11 (73%)	5 (11%)	22.0 (5.0-96.1)	<0.001	0 (0%)
Abnormal reflexes	9 (60%)	6 (14%)	9.5 (2.4-36.5)	0.001	1 (1.7%)
Cranial nerve palsy	6 (50%)	2 (4%)	21.5 (4.0-123.5)	<0.001	3 (5.0%)
Increased tone	10 (67%)	5 (11%)	15.6 (3.7-64.6)	<0.001	1 (1.7%)
Illness length > 7 days	7 (58%)	5 (16%)	8.96 (2.0-39.6)	0.004	11 (18.3%)
<i>Median (days)</i>	12	2.5			
Serum sodium ≤132 mmol/L	10 (83%)	4 (9%)	50.0 (8.0-312.7)	<0.001	4 (6.7%)
<i>Median (mmol/L)</i>	131	135			
CSF white cell count ≥18 cells x10 ⁶ /L	9 (60%)	7 (16%)	7.7 (2.1-28.7)	0.002	2 (3.3%)
<i>Median (cells x10⁶/L)</i>	25	2			
CSF lymphocytes ≥10 cells x10 ⁶ /L	9 (60%)	8 (18%)	6.6 (1.8-23.7)	0.006	2 (3.3%)
<i>Median (cells x10⁶/L)</i>	15	0			
CSF protein ≥0.65g/L	11 (73%)	6 (14%)	17.4 (4.2-72.9)	<0.001	1 (1.7%)
<i>Median (g/L)</i>	0.85	0.20			
CSF glucose ≤2.3 mmol/L	7 (50%)	7 (16%)	5.4 (1.4-20.4)	0.009	1 (1.7%)
<i>Median (mmol/L)</i>	1.6	3.6			
CSF chloride ≤119 mmol/L	10 (71%)	14 (36%)	5.2 (1.4-19.5)	0.014	3 (5.0%)
<i>Median (mmol/L)</i>	110	121			

*Odds ratio calculated from available data and significance determined using Fisher's exact test; †Missing data calculated using number missing fields for each variable among development group of cases and controls

Figure 1. **A novel rapid clinical decision tool to identify TBM: CHILD TB LP**

The CHILD TB LP Clinical Decision Tool (Maximum possible points = 9)	
Entry Criteria	Age 3-months to 15-years old with suspected CNS infection in a TB endemic area
C H I L D T B L P	<u>C</u> onsciousness, altered <u>H</u> IV-infected caregiver <u>I</u> llness Length >7 days <u>L</u> ethargy, chronic fatigue or reduced playfulness <u>D</u> eficit in focal neurology which is new <u>T</u> hrive, failure to <u>B</u> lood/serum sodium ≤ 132 mmol/L <u>L</u> ymphocytes (CSF) ≥ 10 cells $\times 10^6/L$ <u>P</u> rotein (CSF) ≥ 0.65 g/L <div> The presence of each variable gives 1 point each The absence of each variable gives 0 points (0 points also if information is not available to assess that variable) </div>
Result	Likely TB Meningitis = ≥ 4 points Unlikely TB Meningitis = ≤ 3 points
Remember	The following investigations should be performed on all children with suspected TBM as a minimum: a) mantoux b) chest x-ray c) sputum/gastric washing for Mtb d) CSF for Mtb <i>& consider neuroimaging depending on clinical presentation & setting</i>