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Evaluation of a simple clinical algorithm to diagnose tuberculous meningitis in adults

Hari KishanBoorugu
Consultant Physician, Yashoda Hospitals, Hyderabad
Former Assistant Professor, Christian Medical College, Vellore, India

Abstract:
Background*: Despite the advent of newer diagnostics to diagnose tuberculous meningitis, clinicians in limited resource settings still rely on simple clinical algorithms.This study was done to validate simple clinical algorithm derived by Rashmi Kumar et al to diagnose tuberculous meningitis.*
Materials and methods: *We did a retrospective study of adult patients admitted with meningitis between March 2003 to April 2005. Patients were diagnosed to have tuberculous meningitis based on a composite criteria involving clinical, CSF, radiological features, histopathology and microbiological reports. Sensitivity and Specificity of Rashmi Kumar's diagnostic algorithm was measured in comparison with final diagnosis.*
Results*: If only one feature of the five clinical predictors mentioned in the algorithm was present, sensitivity and specificity for TBM were 99% and 29% respectively. If 3 features were present, sensitivity and specificity were 35% and 85% respectively.*
Consclusion*: If we use presence of one feature to diagnose TBM, we will be treating a large numbers of patients with anti-tuberculosis treatment unnecessarily exposing them to drug toxicity. If we use presence of 3 features to diagnose TBM, we will miss the diagnosis in a large number of TBM patients. This clinical algorithm does not appear to be a good tool to diagnose TBM but may help exclude TBM if none of the five clinical predictors are present.*
Key words: *Rashmi Kumar algorithm, tuberculous meningitis*

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I. Introduction

Tuberculosis (TB) is highly prevalent in developing countries like India. Tuberculous meningitis (TBM) is a dreaded form of extra pulmonary tuberculosis. Delay in diagnosis and treatment of TBM can result in increased morbidity and mortality.[1] Mycobacterial culture which is the gold standard test for diagnosis of TBM has poor sensitivity and it takes a few weeks to get the result.[1] Nucleic acid amplification tests (NAAT) have their share of limitations.[1] In resource poor settings, we still largely rely on clinical and cerebrospinal fluid (CSF) features to diagnose TBM. Thwaites' diagnostic score and Rashmi Kumar's diagnostic algorithm are a few such diagnostic algorithms based on clinical and/or CSF features. While Thwaites' diagnostic score is widely used, not many are aware of Rashmi Kumar's diagnostic index. We validated this diagnostic index in our adult patients with meningitis.

II. Methodology

Study design: This was a retrospective study done in a tertiary referral teaching hospital in South India. All the patients with the clinical and CSF suggestive of meningitis admitted to adult medical wards between March 2003 and April 2005 were included in this study. Their clinical status and CSF AFB cultures were followed up at 8 weeks. Data was collected from Medical records. Institutional Review board (IRB) protocols were followed.

Inclusion Criteria: All patients with meningitis (as suggested by CSF picture i.e., 10 cells or more permm^3 with CSF sugar less than 50% of concomitant blood sugar) admitted to adult medical wards were enrolled in the study. Sensitivity, Specificity of the proposed diagnostic algorithm were calculated using simple 2 X 2 tables.

Exclusion Criteria: Patients were excluded

1. if they received treatment for both pyogenic (for a minimum of 5 days) and tuberculous meningitis.
2. Patients with CSF sugar >50% of concomitant blood sugar
3. HIV patients with fungal meningitis

Patients with culture proven meningitis or with corroborative evidence i.e., evidence of tuberculosis outside central nervous system were included in the study irrespective of the treatment received and the outcome.
Rashmi Kumar's diagnostic algorithm includes following clinical and CSF features.[2]
1) prodromal stage lasting 7 days or longer
2) optic atrophy on fundal examination
3) focal deficit
4) abnormal movements, and
5) CSF leukocytes comprising less than 50% polymorphs.

In the original study done by Rashmi Kumar et al, Sensitivity and specificity of this diagnostic algorithm for TBM were 98.4% and 43% respectively if atleast one feature was present, 54% and 98% respectively if 3 or more werepresent.[2]

We compared this diagnostic algorithmagainst the final diagnosis of TBM usingthe following criteria:

The diagnosis of TBMwas made if mycobacterium tuberculosis was isolated from CSF (smear or culture positivity) or if the computerized tomography scanof brain showed features suggestive of tubercular meningitis (hydrocephalus, basal exudates), chest radiography suggestive of active pulmonary tuberculosis or evidence of tuberculosis outside central nervous system (eg.sputum positive for acid fast bacilli(AFB), other tissues like lymph nodes positive for AFB or with granulomatous inflammation suggestive of tuberculosis on histopathology).A good response to antitubercular therapy (ATT) in the form of symptomatic improvement of headache, fever, altered sensorium at the end of 2 months was also considered diagnostic of TBM. Post meningitic sequelae were not considered as lack of treatment response.

Bacterial meningitis was diagnosed if the pathogenic bacteria was isolated from CSF (smear or culture positivity) or with clinical meningitis with all of the following features:

Low concentration of glucose in CSF (<50% of that in blood)
Lymphocytes and neutrophils in CSF
Recovery without anti tuberculosis chemotherapyat 4 weeks after admission.
There were 281 patients with meningitis admitted to the medical wards between March 2003 and April 2005(excluding HIV infection patients with fungal meningitis). Out of this, 131 patients were enrolled in the study.

III. Results

150 patients were excluded for the following reasons:
1. 34 patients - as they received treatment for both pyogenic meningitis and tuberculous meningitis (antibiotics + ATT)
2. 19 patients - as complete data was not available (this included patients for whom only ventricular CSF results were available)
3. 13 patients with aseptic meningitis
4. 9 patients who were discharged against medical advice or died.
5. 62 patients - due to lack of follow up.
6. 13 patients - as their CSF/blood sugar >50% (though they were were diagnosed to have either pyogenic or TBM by the treating physician).

Table 1 summarizes the criteria supporting diagnosis of TBM. CT brain was suggestiveof TBM in 28 cases, evidence of pulmonary TB and extra pulmonary TB (besides CNS TB) was seen in one third of patients. CSF AFB culture was positive in 21 patients and TBM diagnosis was made in 34 patients based on treatment response.

Table 2compared various clinical and CSF features in both TBM and bacterial meningitis group.As expected, significant difference was found between both groups in terms of duration of illness, white blood cell count, CSF white cell count, CSF neutrophil percentage and incidence of hyponatremia. Of the 5 independant predictor's of TBM in Rashmi Kumar's algorithm, only prodromal stage of more than or equal to 7 days and presence of optic atrophy were found to be predictive of TBM in this study (table 3). CSF culture was positive in 21% in TBM groupand in 52% in bacterial meningitis group(table 4).

Table 1: Criteria supporting diagnosis of TBM

Criterion	Number of cases
CT brain characteristics TBM	28
Coexisting Pulmonary tuberculosis	16
Extra pulmonary tuberculosis besides CNS involvement	18

CSF Culture showing AFB growth	21
Diagnosis based on treatment response	34

Table 2: Patient characteristics and CSF findings in TBM &pyogenic meningitis

	TBM (n=97)		Pyogenic meningitis (n=27)		
	Mean	Median	Mean	Median	p
Age in years	33.6	31	47.9	52	
Blood WBC counts	10438.9	9700	17507.6	15650	<0.001
Duration of illness in days	55	30	4.48	4	<0.001
CSF WBC count in cu.mm	383.9	220	3599.5	980	0.001
CSF neutrophil %	19	7	73.9	91	0.009
Duration of fever in days	41.9	20	4	3	<0.001
Duration of headache in days	35.8	15	3.75	3.5	<0.001
Serum sodium in meq/l	129.8	132	136.3	136.5	<0.001
CSF sugar in mg/dl	34	33.5	36.2	25	0.001
CSF protein in mg/dl	275	169.5	416.3	370.5	0.747
CSF sugar/blood sugar ratio	26.9	26.9	22.8	20	0.137
					0.255

*NOTE: data is not available for all the patients, eg. ratio of CSF sugar/ blood sugar is available only for 59 patients in TBM group.
P is p value for difference between means.

Table 3: Predictors of TBM as per Rashmi Kumar's diagnostic index

	TBM		Pyogenic meningitis		P value
Prodromal stage in days					
	n	%	n	%	
>=7 days	88	89.7	8	29.6	<0.001
<7days	10	10.2	19	70.3	
Total	98	100	27	100	
Optic atrophy					-
	n	%	n	%	
Present	11	11.2			
Absent	83	84.6	27	100	
Total	94	95.9			1.0
Focal deficits					
	n	%	n	%	
Present	21	21.4	5	18.5	
Absent	77	78.5	22	81.4	0.573
Total	98	100	27	100	
Abnormal movements					
	N	%	n	%	
Present	16	16.3	6	22.2	1.1
Absent	80	81.6	21	77.7	
Total	96	97.9	27	100	

Cranial nerve palsies					
	N	%	n	%	
Present	16	16.3	4	14.8	
Absent	81	82.6	22	81.4	
Total	97	98.9	26	96.2	

Table 4: CSF culture positivity in TB and pyogenic meningitis

CSF culture	TBM		Pyogenic meningitis	
	Number	%	N	%
positiive	21	21.6	14	51.8
negative	76	78.4	13	48.2
total	97	100	27	100

Table 5: Diagnostic accuracy ofRashmi Kumar's algorithm
Patient is diagnosed to have TBM if 3 clinical predictors are present

	FINAL DIAGNOSIS			
		TBM	NON TBM	Total
Diagnosis byRashmiKumar'salgorithm	postivie	34	5	39
	negative	63	29	92
				131

Sensitivity for TBM = (34/97)x100 = 35% (if atleast 3 features are present)
Specificity for TBM = (29/34)x100 = 85.3% (if atleast 3 features are present)
If only one clinical predictor is present, sensitivity -99%, specificity - 29%

IV. Discussion

Most clinicians rely on clinical and CSF features to diagnose TBM. CSF mycobacterial cultures which is the gold standard to diagnose TBM has poor sensitivity and it takes a few weeks to obtain the culture report and delay in initiation of antituberculosis treatment (ATT) is associated with increase in morbidity and mortality.[1]However, culture yield is only between 23 to 49%.[3]NAAT are quick but expensive and availability is an issue. TatianaMetcalf et al (2018) evaluated GeneXpertMTB/RIF in TBM patients and sensitivity was found to be 23% in clinically diagnosed TBM group and 88% in definite TBM group.[4] Sensitivity of GeneXpertMTB/RIF in various studies varied from 23 to 59%.[3]

In view of above mentioned limitations, most clinicians rely on clinical and CSF features todiagnose TBM. Thwaites' diagnostic score is one such score with reasonable diagnosticaccuracy to differentiate TBM from bacterial meningitis (sensitivity and specificity of 86% and 79% respectively).[1] Lancet consensus scoring system includes clinical, CSF and radiologicalfeatures to diagnose TBM and probably is the most widely accepted now.[5]

However, in resource poor settings, radiological and NAAT availability is an issue and we attempted to relook at an old clinical diagnostic algorithm developed by Rashmi Kumar et al. If only one feature of the five clinical predictors mentioned in the algorithm was present, sensitivity and specificity for TBM were 99% and 29% respectively. If 3 features werepresent, sensitivity and specificity were 35% and 85% respectively. If we use presence of one feature to diagnose TBM, we will be treating a largenumbers of patients with ATT unnecessarily exposing them to drug toxicity. If we use presence of 3 features to diagnose TBM, we will miss the diagnosis in a large number of TBM patients which is dangerous!

V. Conclusion

In current scenario, best way to diagnose TBM is using a composite algorithm including clinical features, CSF findings, radiological findings and microbiology (smear, culture and NAAT). However, in resource poor settings we need simple clinical algorithms (eg Thwaites' diagnostic score) which have reasonable accuracy to diagnose or to exclude TBM. Clinical algorithm derived by Rashmi Kumar et al does not

appear to be a good tool to diagnose TBM but may help exclude TBM if none of the five clinical predictors are present.

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