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Research Article

USEFULNESS OF CSF-ADA AS AN ANCILLARY TOOL IN THE DIAGNOSIS OF TBM

Virendra Atam., Arpit Gupta* and Gyan Ranjan Nayak

Department of Medicine, KGMU, Lucknow

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A B S T R A C T

Introduction: Tuberculous meningitis (TBM) is a global health issue and is the most severe form of extrapulmonary tuberculosis with high mortality and morbidity. Even after many years of experience with the disease, the definitive diagnosis of TBM remains a problem. Adenosine Deaminase enzyme is produced by lymphocytes and monocytes and reflects cell-mediated immunity. The enzyme is estimated easily by the colorimetric method. Generally, ADA assays may be useful in confirming TBM, but raised levels may also be seen in other CNS disorders (sarcoidosis, meningeal lymphoma, subarachnoid hemorrhage, neurobrucellosis), rendering it too nonspecific.

Aim: To evaluate the role CSF-ADA in the diagnosis of tuberculous meningitis as an ancillary tool.

Materials and Methods: The study was a prospective study, done in the department of medicine and department of neurology from September 2015 to August 2016. The patients who got admitted with the clinical picture of Meningitis in Medicine and Neurology department were assessed on Thwarts Criteria and those found to be likely cases of T.B.M, as per the criteria were included in the study and their CSF-ADA levels were measured.

Results: CSF ADA levels ranged from 8 to 251 units with a mean value of 32.97±40.863 and median of 20.40. ADA levels of patients with Thwaite's score -3 to 0 were significantly lower (19.20±14.41) as compared to those of patients with Thwaite's score -5 (43.54±50.54). Statistically, this difference was significant too (p=0.003).

Conclusion: CSF ADA levels were found to be above 10 IU/L in 86 patients enrolled and presumptively diagnosed as TBM based on the Thwaite's criteria. Thus the sensitivity was found to be 86.9 %, suggesting its importance as an ancillary tool for the diagnosis of TBM.

INTRODUCTION

Tuberculous meningitis (TBM) is a global health issue and is the most severe form of extrapulmonary tuberculosis with high mortality and morbidity. Its reported prevalence varies from 5 to 15% in various cohorts of the population of patients with tuberculosis (Farer *et al* 1979, Wood *et al* 1998). One-third of the world's population is infected with latent TB. These individuals are not clinically affected but carry a lifetime risk of 10% for developing active disease. [(1)]There were an estimated 8.6 million incident cases of TB globally in 2012, with 1.3 million deaths.[(2)] Clinically, TBM is a syndrome of sub-acute lymphocytic meningitis in the majority of patients. In developing countries, TB meningitis is still a disease of childhood with the high incidence in the first three years of life (Tandon PN, Brattier R,a handbook of clinical neurology, Donald PR) Tuberculous meningitis (TBM) can occur as the sole manifestation of TB or concurrent with pulmonary or other extrapulmonary sites of infection. [(3-5)] Even after many years of experience with the disease, the definitive diagnosis of TBM remains a problem. Early diagnosis and treatment of TBM are necessary because in the untreated patients the mortality is 100% in 5 to 8 weeks (Molavi and Le Frock 1985). The key to the diagnosis is the examination of CSF. The presumptive diagnosis of TBM is made when CSF shows lymphocytic predominance with increased protein and decreased sugar with the absence of usual organisms on Gram staining and aerobic cultures, but the "gold standard" for diagnosis remains the identification of Mycobacterium tuberculosis in the CSF by direct staining of culture.

Adenosine Deaminase enzyme is produced by lymphocytes and monocytes and reflects cell-mediated immunity. The enzyme is estimated easily by the colorimetric method. Iso-enzyme ADA 2 is present only in macrophages and monocytes and they release it when stimulated in the presence of live microorganisms in their interior. This is why ADA 2 is increased in biological fluids in the course of infectious diseases characterized by microorganisms infecting the macrophages (such as the Tubercle bacillus). [(6)] A recent meta-analysis concluded that the mean sensitivity and specificity of ADA assays were 79 and 91%, respectively[(10)]. Generally,

Corresponding author:* **Arpit Gupta
Department of Medicine, KGMU, Lucknow

ADA assays may be useful in confirming TBM, but raised levels may also be seen in other CNS disorders (sarcoidosis, meningeal lymphoma, subarachnoid hemorrhage, neurobrucellosis), rendering it too nonspecific. [7,8,9] It is not a useful test in HIV-positive patients. [7] So this study was done to evaluate the role CSF-ADA in the diagnosis of tuberculous meningitis as an ancillary tool.

MATERIALS AND METHODS

The study was a prospective study, done in the department of medicine and department of neurology from September 2015 to August 2016. The patients who got admitted with the clinical picture of Meningitis in Medicine and Neurology department were assessed on Thwarts Criteria and those found to be likely cases of T.B.M, as per the criteria were included in the study and their CSF-ADA levels were measured.

Inclusion Criteria

1. Those subjects who give informed consent for the study.
2. Patients fulfilling the diagnostic criteria of TBM based on the Thwarts criteria.

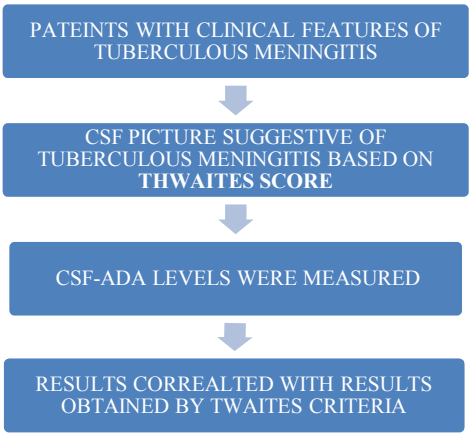
Exclusion Criteria

1. Patients/attendants refusing consent.
2. Patients not fulfilling the Thwaites criteria.
3. Brain abscess
4. Head trauma

Table 1 Thwaites Criteria

Parameters		DI
Age	>= 35 years	2
	< 35 years	0
Blood WBC, 10^3 / ml	>= 15000	4
	< 15000	0
History of illness, days	>= 6 days	-5
	< 6 days	0
CSF total WBC, 10^3 / ml	>= 900	3
	< 900	0
CSF % neutrophils	>= 75 %	4
	< 75 %	0
DI > 4: TBM		
DI 1-4 : other bacterial meningitis		

Study design: Patients who presented with history and clinical features suggestive of TBM were included in this study. A criterion suggested by Thwaites *et al* [3] was used to label these patients to be suffering from TBM. Patients satisfying the criteria thus, labeled as TBM were further evaluated. CSF-ADA values were measured in these patients, and the results were correlated with the results obtained via Thwaites criteria.



RESULTS

Table 2 Descriptive statistics for CSF ADA

	Minimum	Maximum	Mean	Std. Deviation	Median
ADA	3	251	32.97	40.863	20.40

CSF ADA levels ranged from 8 to 251 units with a mean value of 32.97±40.863 and median of 20.40.

Table 3 Distribution of cases according to Thwaites Score

SN	Score	No. of cases	Percentage
1	-5	56	56.6
2	-4	0	0
3	-3	39	39.4
4	-2	1	1.0
5	-1	2	2.0
6	0	1	1.0

Table 4 ADA Correlation with Thwaite's Score

Thwaite's scores	No. of cases	Mean	SD	Minimum	Maximum
-5	56	43.54	50.54	6.60	251.00
-3 to 0	43	19.20	14.41	2.70	92.50
Total	99	32.97	40.86	2.7	251

F=9.370; p=0.003

ADA levels of patients with Thwaite's score -3 to 0 were significantly lower (19.20±14.41) as compared to those of patients with Thwaite's score -5 (43.54±50.54). Statistically, this difference was significant too (p=0.003).

Table 5 Sensitivity of ADA (>10 units) for Thwaites score <4

ADA Levels	Thwaites score		Total
	<4	>4	
>10 units	86	0	86
<10 units	13	0	13
	99	0	99

Sensitivity = 86.9%; Specificity=NA; PPV=100%; NPV=0%; Accuracy=86.9%

DISCUSSION

Due to lack of a single simple diagnostic test, for being considered the gold standard for diagnosis of TBM, a score suggested by THWAITES *et al*[3]. was used which comprises age, history of illness blood TLC, CSF % Neutrophils and CSF-TLC. A score =or < 4 is considered as TBM. The Thwaite's scoring as a diagnostic criterion has been shown to be of the range of approximately 95% and has been validated.in large series. The lower the score, the higher the probability, suffering from TBM. 56.56% (n=56) had a Thwaite's -5. It was 43.43% (n=43) in patient having a Thwaite's score 0f -3 to 0.CSF ADA levels above 10 IU/L were taken to be positive. It was higher (>10 IU/L) in 86 patients with a sensitivity of 86.9%; among all the cases of TBM according to the Thwaite's criteria.The lower the Thwaite's score, the more is its predictive value in the diagnosis of TBM. Patients with the lowest possible Thwaite's score (-5, n=56) had mean ADA of 43.54. Those with a higher score(-3 and more) had mean ADA at 19.20. This was statistically significant too(p=.003).

CONCLUSION

CSF ADA levels were found to be above 10 IU/L in 86 patients enrolled and presumptively diagnosed as TBM based on the Thwaite'scriteria. Thus the sensitivity was found to be

86.9 %. Hence, suggesting its importance as an ancillary tool for the diagnosis of TBM.

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