Critical Cerebrospinal Fluid Adenosine Deaminase Activity In Tubercular Meningitis

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Abstract: Background: Tuberculosis of the central nervous system accounts for ~5% of extra pulmonary cases in the United States. It is seen most often in young children but also develops in adults, especially those infected with HIV. If unrecognized, tuberculous meningitis is uniformly fatal. This disease responds to chemotherapy. Cerebrospinal fluid (CSF) evaluation is the single most important aspect of laboratory diagnosis of meningitis. Basic studies of CSF that should be performed in meningitis include measurement of pressure, cell count and differential count, estimation of glucose and protein levels, Gram's stain and culture. Objectives: To evaluate the diagnostic significance of CSF adenosine deaminase (ADA) activity in tuberculous meningitis. Material & Methods: 70 Tubercular Meningitis patients who were admitted in Department of Medicine, Victoria hospital were included. The study was approved by the Ethical Committee of Bangalore Medical College and Research Institute, Bangalore. Patients were selected after fulfilling the following inclusion and exclusion criteria. Results: The mean age of the 70 patients studied was 39.82+16.48 years. The youngest patient was 18 years old and oldest patient was 70 years. The mean value of ADA activity in tubercular meningitis was 18.07±8.03IU/L. Cut-off value of ADA in our study was 10 IU/. The result was statistically significant with a p value<0.001. Conclusion: The test for ADA in CSF is simple and can be carried out in a central laboratory with a rapid diagnosis, thus reducing unwarranted or harmful therapy for patients. Elevated CSF-ADA level helps in differentiating tubercular from non-tubercular meningitis. [Nipanal A Natl J Integr Res Med, 2021; 12(1):12-16]

Key Words: CSF- cerebrospinal fluid, ADA- adenosine deaminase, tubercular meningitis

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Introduction: Tuberculosis of the central nervous system accounts for ~5% of extrapulmonary cases in the United States. It is seen most often in young children but also develops in adults, especially those infected with HIV. Tuberculous meningitis results from the hematogenous spread of primary or postprimary pulmonary tuberculosis or from the rupture of a sub ependymal tubercle into the subarachnoid space. In more than half of cases, evidence of old pulmonary lesions or a miliary pattern is found on chest radiography.[1]

If unrecognized, tuberculous meningitis is uniformly fatal. This disease responds to chemotherapy; however, neurologic sequelae are documented in 25% of treated cases, in most of which the diagnosis has been delayed.[1]

The disease often presents subtly as headache and slight mental changes after a prodrome of weeks of low-grade fever, malaise, anorexia, and irritability.[(1)]Lumbar puncture is the cornerstone of diagnosis. In general, examination of cerebrospinal fluid (CSF) reveals a high leukocyte count (up to 1000/µL), usually with a predominance of lymphocytes but sometimes with a predominance of neutrophils in the early stage; a protein content of 1–8 g/L (100–800 mg/dL); and a low glucose concentration.

However, any of these three parameters can be within the normal range. AFBs are infrequently seen on direct smear of CSF sediment, and repeated lumbar punctures increase the yield. Culture of CSF is diagnostic in up to 80% of cases and remains the gold standard. [1]

In humans, the highest ADA activity is found in thymus and other lymphoid tissues (~800I,/,.lU/L) and the lowest in erythrocytes (~1IU/L).

Among non-lymphoid tissues in human, relatively high levels of ADA are found in the villi of epithelial cells lining the duodenum; levels are lower in the other portions of the gastrointestinal tract.

Tissues such as muscle, liver, kidney, brain and blood have low activity in most species.[2]

The activity of ADA is subject to changes depending upon the degree of activity of the cell i.e. whether differentiation or proliferation occurs.[2] The definitive diagnosis of tuberculous meningitis depends on the detection of acid fast bacilli (AFB) and culture of Mycobacterium Tuberculosis from CSF. AFB is seen on direct smear of CSF sediment in only 20% of the cases.

However, it takes 4-8 weeks for the bacilli to be grown in culture. Even the characteristic of CSF cytological and biochemical changes is also variable and be even absent.3 Hence, there is a need for a simple,rapid, accurate, and specific test to confirm the diagnosis of tuberculous meningitis.

Hence this study is undertaken to evaluate the diagnostic significance of CSF adenosine deaminase (ADA) activity in tuberculous meningitis.

Materials & Methods: Seventy tubercular meningitis patients who were admitted in Department of Medicine, Victoria hospital were included. The study was approved by the Ethical Committee of Bangalore Medical College and Research Institute, Bangalore. Patients were selected after fulfilling the following inclusion and exclusion criteria.

Inclusion Criteria: Age > 18 years. Clinical features suggestive of meningitis.

Exclusion Criteria: Age < 18 years. Associated severe hepatic dysfunction. Severe dyslipidemia. Females on oral contraceptives and intrauterine device. Patients in whom lumbar puncture is contraindicated.

The patients were assessed clinically and with laboratory investigations - complete heamogram, LFT, RFT, RBS, serum electrolytes, HIV test, chest X-ray, CT brain(plain) were recorded. CSF Cytology, Biochemistry, Gram stain, AFB stain, & Culture were done. An estimation of CSFADA was done for all the patients.

Criteria For Diagnosis Of Tubercular Meningitis:

Clinical Features: Insidious in onset, may be associated with tuberculosis of other organs, signs of meningeal irritation.

CSF Analysis Showing: Pleocytosis of > 60 cells/mm^3, predominantly lymphocytes. Proteins >40mg/dl. Sugar < 40mg/dl. AFB stain or culture positive.

Neuroimaging Showing: Evidence of Meningeal enhancement, basal exudates and/or tuberculoma.

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented in Mean SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

The following assumptions on data have been made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, and Cases of the samples should be independent.

Significant Figures:
+ Suggestive significance (P value: 0.05<P<0.10)
* Moderately significant (P value: 0.01<P< 0.05)
** Strongly significant (P value: P<0.01)

Statistical Software: The Statistical software namely SAS 9.2, SPSS 15.0, ,MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

Result: 70TubercularMeningitis patients who were admitted in Department of medicine are included in the study. The mean age of the 70 patients studied was 39.82±16.48 years. The youngest patient was 18 years old and oldest patient was 70 years. Maximum patients in the study were aged between 21-40. Table 1

Table 1: Age Distribution of Patients

Age (Years)	Tubercular Meningitis	In percentage (%)
18-20	10	14.28
21-40	34	48.57
41-60	17	24.29
>60	09	12.86
Total	70	100

In this study, 58.57% were Male and 41.43% were Female. The mean cell count is 308.57±252.17 Table 2

Table 2: CSF Analysis – Cell Count

Cell Count (Per Cu mm)	Tubercular Meningitis
< 100	22
100- 1000	39
>1000	09
Total	70
Mean Value ± SD	308.57±252.17

The mean lymphocyte count in tubercular meningitis is 86.24±28.20. Table 3

Table 3: CSF Analysis – Lymphocytes

Lymphocytes (%)	Tubercular Meningitis
0-10	03
11-20	01
21-30	01
31-40	02
41-50	01
51-60	03
61-70	04
71-80	15
81-90	32
91-100	8
Mean ± SD	86.24±28.20

Mean polymorphs in tubercular meningitis is 16.76±26. Table 4

Table 4: CSF Analysis – Polymorphs

Polymorphs (%)	Tubercular Meningitis
0-10	26
11-20	27
21-30	08
31-40	06
41-50	01
51-60	01
61-70	00
71-80	00
81-90	01
91-100	00
Mean ± SD	16.76±26

Mean protein in tubercular meningitis is 204.42±132.97mg/dl, Z=2.087 P≤0.037 which is moderately Significant. Table 5

Table 5: CSF Analysis – Protein

Protein (mg/dl)	Tubercular Meningitis
0 – 100	04
101 – 200	29
201 – 300	24
301 – 400	09
401 – 500	03
>500	01
Mean Value ±SD	204.42±132.97

The mean value of ADA activity in tubercular meningitis was 18.07±8.03IU/L. Cut-off value of ADA in our study was 10 IU/. The result was statistically significant with a p value<0.001.

Discussion: Tuberculosis continues to be a major health problem of developing countries like India. Neuro tuberculosis is the most dreaded complication. Tuberculous meningitis is the commonest manifestation of neuro tuberculosis.
A review of literature has shown that CSF ADA levels could differentiate various types of meningitis. Over the last decade or so, various investigators have shown that the cut-off levels of ADA could be sensitive and specific for tubercular meningitis.

Ribera et al proposed a cut-off value 9U/l and showed a high sensitivity of (1.0) and specificity (0.99).[7]

The enzymatic activity, as well as progression of the disease was studied in 32 patients with tuberculous meningitis.

A significant rise in levels of enzymes was observed during the first 10 days of therapy, was followed by a gradual decline, and reached normal values after 3 to 4 months of treatment.[7]

Sang-Ho Choi et al studied ADA activity in CSF of 182 patients with meningitis. The mean ADA level in the tuberculous meningitis group was 12.7±7.5 U/L and it was significantly higher than the other groups (3.10±2.9U/l; p<0.001).

The sensitivity and specificity was 0.83 and 0.95 respectively when a cut-off value of 7U/L was used.[4]

Petterssonet al reports sensitivity of 1.0 and specificity of 0.99 when a cut-off value of 20 U/L was used, but in that study there were only 3 enrolled tuberculous meningitis patients.[5]

Chotmongkol V et al identified a CSF ADA level of 15.5 U/l as the best cut-off value to differentiate tuberculous meningitis and non-tuberculous meningitis, with a sensitivity of 75% and specificity of 93%. When tuberculous meningitis

was compared with aseptic and carcinomatous meningitis, a CSF ADA level of 19.0 U/l was the best cut-off value for differentiation, with a sensitivity of 69% and a specificity of 94%.[6]

From above discussion elevated CSF-ADA level in meningitis patient highly suggest Tubercular meningitis. Present study found that CSF-ADA level was significantly increased in tubercular meningitis. The mean value of CSF ADA was 18.07±8.03IU/L. P≤0.001 which is stastically significant.

The sensitivity and specificity of CSF ADA was 92.4%and 100% respectively, with accuracy of 95% with respect to tubercular meningitis when a cut-off value of CSF ADA of 10 IU/L was used.

Table 6: Showing The Various Studies On CSF-ADA With The Cut-Off Values Used; And Sensitivity And Specificity Obtained

Study	Number Of Patients Diagnosed Withtbm	ADA Cut-Off Level (IU/L)	Sensitivity	Specificity
Rajendra Prasad et al[8]	29	3.3	100%	97.87%
Kashyap et al[12]	117	11.39	82%	83%
Gautum N et al[11]	20	6.97	85%	88%
Pettersson et al[5]	3	20	100%	99%
Chotmongkol et al[6]	16	15.5	75%	93%
Choi et al[4]	36	7	83%	95%
Ribera et al[7]	32	--	100%	99%
Lopez et al[9]	--	10	48%	100%
Rohani MY et al[10]	14	9	--	87.69%
Present study	70	10	92.4%	100%

Conclusion: The test for ADA in CSF is simple and can be carried out in a central laboratory with a rapid diagnosis, thus reducing unwarranted or harmful therapy for patients. Cut-off value of CSF ADA in our study was 10 IU/. The result was statistically significant with a p value<0.001., sensitivity and specificity was 92.4% & 100% respectively. Hence elevated CSF-ADA level helps indifferentiating tubercular from non-tubercular meningitis

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