

A Hospital Based Study on Estimation of Adenosine Deaminase Activity (ADA) in Cerebrospinal Fluid (CSF) in Various Types of Meningitis

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ABSTRACT

Objective: Tuberculosis kills 3.70 lakh patients in India every year, out of which 7-12 % are meningeal involvement. Delay in its diagnosis and initiation of treatment results in poor prognosis and sequel in up to 25% of cases. The aim of the present study is to look for a simple, rapid, cost effective, and fairly specific test in differentiating tubercular aetiology from other causes of meningitis. In the present study we measured the adenosine deaminase activity (ADA) in Cerebrospinal Fluid (CSF) of Tubercular Meningitis (TBM) and non-TBM patients.

Methods: Fifty six patients attending hospital with symptoms and signs of meningitis were selected and divided into three groups: tubercular, pyogenic, and aseptic meningitis, depending upon the accepted criteria. CSF was drawn and ADA estimated.

Results: Out of 32 tubercular patients, 28 had CSF-ADA at or

above the cut-off value while four had below. Out of 24 non-tuberculous patients (pyogenic and aseptic meningitis), two aseptic meningitis (AM) patient had ADA levels at or above the cut-off value while 22 had below this value. Results of our study indicate that ADA level estimation in CSF is not only of considerable value in the diagnosis of TBM, CSF, and ADA level 10 U/L as a cut-off value with sensitivity 87.5% and specificity 83.33% and positive predictive value of the test was 87.5%. and 83.3% negative predictive value.

Conclusion: It can be concluded that ADA estimation in CSF is not only simple, inexpensive and rapid but also fairly specific method for making a diagnosis of tuberculous aetiology in TBM, especially when there is a dilemma of differentiating the tuberculous aetiology from non-tuberculous ones. For this reason ADA estimation in TBM may find a place as a routine investigation.

Keywords: Adenosine Deaminase Activity (ADA), Cerebrospinal Fluid (CSF), Tubercular Meningitis (TBM), Non-tuberculous meningitis

INTRODUCTION

Meningitis is defined as an inflammatory response to bacterial and non bacterial infection of the pia, arachnoid and CSF of the subarachnoid space. In the first category, the most common types are pyogenic (bacterial) meningitis and TBM. In the second category the most common type is viral meningitis (VM).

TBM is an endemic disease in developing countries [1]. At present 1/5th of the global annual new cases occur in India. Tuberculosis claims 100 lives per day, out of them 20% patients have TBM. Delay in diagnosis and so in the start of effective treatment results in poor prognosis and sequelae in up to 25% of cases [2]. Available methods of diagnosis of TBM were evaluated [3] and all of them were found to have low sensitivity and specificity [4-5]. There are several methods to diagnose tuberculous meningitis with accuracy like CSF culture, CSF Polymerase Chain Reaction (PCR), but these methods are time consuming and costly respectively. In the developing countries which have lower socio-economic patients, which cannot afford expensive laboratory investigation. So we required a diagnostic stool for inexpensive and early detection of TBM.

ADA is an enzyme involved in purine metabolism that catalyzes the deamination of adenosine, forming inosine in the process [6]. It is considered as an indicator of cell-mediated immunity and is found mainly in T-lymphocytes [7]. The chief physiological function of ADA is related to lymphocyte proliferation and differentiation and its activity is found to be elevated in those disease in which there is a cell mediated immune response [8]. Numerous previous studies had demonstrated that CSF-ADA estimation is useful in the diagnosis of TBM and can differentiate TBM from normal subjects or from

patients with other neurological disorder [9-11]. However, the results were variable and one study has shown that ADA is of limited value as it is also raised in other types of meningitis especially Pyogenic Meningitis (PM) [12].

In view of these observations, this research was undertaken to know how far the CSF-ADA activity varies in various types of meningitis and to know its diagnostic value for TBM (sensitivity and specificity). A cut-off value of CSF-ADA activity has been calculated for diagnosis of TBM.

MATERIALS AND METHODS

The study was conducted at Patna Medical College and Hospital, Patna, Bihar, India, in 56 adult patients (of age 15 years and above) of meningitis of varied aetiology admitted in the medical ward and emergency over a period of last two years (2009-2011). The diagnosis of meningitis was established by detailed clinical history, neurological examination and laboratory findings, and patients were segregated into three groups:

Group A-Tuberculous meningitis (TBM) (n32), Group B-Pyogenic meningitis (PM) (n12), Group C-Aseptic meningitis (AM) (n12).

Criteria for Diagnosis of Cases

Tuberculous meningitis (TBM)—The disease is gradual in onset with symptom like apathy, anorexia, weakness, and prolonged low grade fever (more than two weeks), signs of meningeal irritation, i.e., headache, vomiting, convulsion, neck rigidity, and Kernig's sign appear later. Confirmation demonstration of primary focus in lung on X-ray chest, increased ESR, CSF clear, colourless,

cobweb formation when left for 12-24 hrs, increased cell count with lymphocytic pleocytosis (>50 cells/mm³), protein more than 60 mg% and sugar less than 2/3rd of corresponding blood sugar. CT scan of brain showing evidence of chronic meningitis like hydrocephalus, basal exudates, infarcts, tuberculomas.

Pyogenic meningitis (PM)—Acute illness and rapidly progressive, history of ear infection or ear discharge or other septic focus, signs of meningeal irritation, i.e., headache, seizure, neck stiffness and Kerning's sign. TLC is increased, predominantly polymorphs, other acute phase reactant may be increased.

CSF-CSF of patient showing organism in Gram's stained smear or culture or presence of bacterial antigen on latex agglutination was taken as diagnostic criteria. In the absence of organism, CSF showed pleocytosis of more than 100 cells/mm³ predominantly polymorphs, sugar less than half of corresponding blood sugar, and protein more than 60 mg% and response to intravenous (IV) antibiotics of 10-14 days.

Aseptic meningitis—Acute onset of fever, muscle ache, seizure and unconsciousness (if associated with encephalitis), signs of meningeal irritations, clear CSF-CSF pleocytosis with more than 10 cells/mm³, predominantly lymphocyte, raised protein and sugar more than 2/3rd of corresponding blood sugar value and absence of organism on Gram's stain or culture.

Sample Collection

CSF samples were collected by standard lumbar puncture. Approximately 3 ml of CSF sample was obtained; 2 ml of sample was used for total and differential cell count, biochemistry and smear for Gram's, Indian ink, acid-fast bacilli (AFB) staining and remaining CSF was used for ADA estimation. All samples were stored at 4°C and estimated within 24 hours.

ADA Activity Measurement

ADA activity in CSF was estimated at 37°C according to the method of Galanti and Giusti colorimetric method based on Chang and Marbach modification of Berthlot reaction, that is formation of coloured indophenol complex from ammonia liberated from adenosine and quantified spectrophotometrically (U.V. visible spectrophotometer Remi Mode C-24). One unit of ADA is defined as the amount of enzyme required to release 1 mmol of ammonia/min from adenosine at standard assay conditions. Results were expressed as units per litre per minute (U/L/min).

STATISTICAL ANALYSIS

Results are expressed as mean \pm SD with Range. To compare the mean ADA activity between the TBM, non-TBM infectious meningitis and non-infectious Neurological disorders groups, the Kruskal-Wallis Test (non-parametric analysis of variance {ANOVA}) with the Dunnett post-test was used. A p-value <0.05 was considered significant. A cut-off value of ADA activity for TBM patients was calculated from the mean plus SD of ADA activity in the non-TBM infectious meningitis group. The sensitivity (true positive rate) for the test was calculated as: (the number of samples in the TBM group with ADA activity \geq (mean \pm SD) of ADA activity in the non-TBM infectious meningitis group divided by the total number of samples in TBM group) \times 100. The specificity (true negative rate) for the test was calculated as: (the number of samples in non-TBM infectious meningitis group with ADA activity < (mean \pm SD) of ADA activity in the non-TBM infectious meningitis group divided by the total number of samples in non-TBM infectious meningitis group) \times 100.

RESULTS

The present study was carried out on 56 patients of meningitis [Table/Fig-1] admitted in medical ward and emergency, Department of Medicine, Patna Medical College and Hospital, Patna, Bihar, India.

[Table/Fig-2] shows that maximum number of cases was in 15-24

years of age group and least in 45 and above years of age group. But there was insignificant variation in CSF-ADA level with respect to age.

The ADA activity in CSF of TBM ranged from 8.6-28 international Units per liter (IU/L) with mean activity of 13.58 IU/L. It was 8.6-28 IU/L in male with mean value of 13.41 IU/L and 9.7-26.3 IU/L in female with mean value of 13.73 IU/L. There was no significant difference in mean CSF-ADA with respect to sex [Table/Fig-3].

S.D.—Standard Deviation; S.E.—Standard Error of mean [Table/Fig-4] shows that CSF-ADA activity was elevated in case of TBM with mean 13.58 \pm 4.54 IU/L while lowered in case of PM (mean 7.68 \pm 2.00 IU/L) and AM (6.72 \pm 2.71 IU/L). There was overlapping of CSF-ADA level between pyogenic and aseptic meningitis [Table/Fig-4].

[Table/Fig-5] shows that there was statistically significant difference in the CSF-ADA levels of TBM and PM (t' = 4.32, p < 0.0001, DF = 42) and also TBM and AM (t = 4.89, p < 0.0001, DF = 42) while no significant difference was observed between pyogenic and aseptic meningitis [Table/Fig-6].

Disease	Number of Cases		
	Male	Female	Total No. of Cases
Tuberculous Meningitis	16	16	32
Pyogenic Meningitis	7	5	12
Aseptic Meningitis	7	5	12

[Table/Fig-1]: Shows sex distribution in patient with meningitis

Age in Year	No. of Cases	CSF-ADA activity IU/L	
		Range	Mean
15-24	14	8.6-28	12.97
25-34	11	9.8-26.3	14.60
35-44	5	10.5-15.5	13.62
45 and above	2	11.2-14.8	13.00
Total	32	8.6-28	13.58

[Table/Fig-2]: Showing age distribution of CSF-ADA value in different age groups in Tuberculous Meningitis (TBM)

Sex	No. of Cases	CSF-ADA activity IU/L	
		Range	Mean
Male	16	8.6-28	13.41
Female	16	9.8-26.3	13.73
Total	32	8.6-28	13.58

[Table/Fig-3]: Showing CSF-ADA activity in TBM with respect to sex

Disease	No. of Cases	Range (IU/L)	Mean (IU/L)	SD	SE Mean
Tuberculous Meningitis	32	8.6-28	13.58	\pm 4.54	0.80
Pyogenic Meningitis	12	4.2-10.4	7.68	\pm 2.00	0.58
Aseptic Meningitis	12	2.2-10.8	6.72	\pm 2.71	0.78

[Table/Fig-4]: Showing CSF-ADA activity in various forms of meningitis

Group	t-value	p-value	Degrees of Freedom (DF)
Tuberculous Meningitis vs Pyogenic Meningitis	4.32	<0.0001	42
Tuberculous Meningitis vs Aseptic Meningitis	4.89	<0.0001	42
Tuberculous Meningitis vs Non-Tuberculous Meningitis (Both)	6.26	<0.0001	54

[Table/Fig-5]: ADA activity in TBM compared with non-tuberculous meningitis

CSF-ADA level (IU/L)	Tuberculous Meningitis	Range (IU/L)		
		Pyogenic Meningitis	Aseptic Meningitis	Total
\geq 10	28	2	2	4
<10	4	10	10	20

[Table/Fig-6]: CSF-ADA efficacy with a cut-off value 10 IU/L

Sensitivity-87.5%, Specificity-83.33%, Positive Predictive Value -87.5%, Negative Predictive Value-83.3%.

[Table/Fig-7] shows that sensitivity and specificity of ADA test in CSF at cut-off 10 IU/L was 87.5% and 83.33% respectively. At higher cut-off ADA value in CSF (11 IU/L) only 24/32 patients were positive for TBM decreasing the sensitivity to 75% from 87.5% while increasing specificity to 100% from 83.33%. At lower cut-off ADA value in CSF (9 IU/L), sensitivity measured to 96.87% but specificity decreased from 83.33% to 66.66%. So ADA levels of 10 IU/L was taken as cut-off value for diagnosis of TBM.

CSF-ADA (IU/L) Cut-off	No. of Patients			Sensitivity (%)	Specificity (%)
	TBM (n=32)	PM (n=12)	AM (n=12)		
9	31	4	4	96.87	66.66
10	28	2	2	87.5	83.33
11	24	0	0	75	100.00

TBM-Tubercular Meningitis, PM-Pyogenic Meningitis, AM-Aseptic Meningitis

[Table/Fig-7]: Sensitivity and specificity of ADA level in CSF of patients different cut-off value of ADA level

DISCUSSION

TBM remains a major global health problem and even in developed countries there is a resurgence of tuberculous infection due to the growing number of people infected with human immunodeficiency virus (HIV) [13,14]. Early confirmatory diagnosis of TBM is difficult to establish because of its pleomorphic clinical pre-sentation [5,15]. Delayed diagnosis and treatment may be associated with many serious Central Nervous System (CNS) complications [16]. The most commonly used laboratory method for the definitive diagnosis of TBM is to demonstrate the presence of tubercle bacilli either by smear and/or culture. However, direct smear methods are often negative in CSF samples and culturing of Maximum Therapeutic Benefit (MTB) takes 4–6 weeks to show the growth [17,18]. Newer methods such as those involving the amplification of bacterial Deoxyribonucleic acid (DNA) by the PCR and comparable systems, are incompletely assessed and not available for widespread use in the developing countries. The sensitivity of the PCR technique varies from 33% to 90% and the specificity from 88% to 100% [19]. Various immunoassays such as antigen and/or antibody detection in CSF samples have been developed with variable sensitivities and specificities [4,8,19-22]. Hence, despite extensive work on TBM, only few diagnostic tests are available. Considering that both humoral and cell-mediated immunity play an important role in TBM infection, it has been suggested that ADA activity in CSF may help differentiate TBM from non-TBM infectious meningitis and non-infectious neurological disorders, and this has been discussed earlier by various workers [10,11].

The present study had been conducted in 56 cases of different form of meningitis. The participant belonged to both sexes and were 15 years and above of age. The observation in various group are discussed as follows:

Tuberculous Meningitis

The 32 cases of TBM, which consisted of 16 males and 16 female of different age were studied. The CSF-ADA value in TBM cases ranged from 8.6 to 28.0 IU/L with mean value of 13.58 IU/L and S.D. \pm 4.54 as shown in [Table/Fig-4]. All the patients except 4 showed higher than cut-off value 10 IU/L of CSF-ADA with sensitivity 87.5% and specificity 83.33%. In addition to this, the positive predictive value of test was 87.5%. Comparative study showed statistically significant difference in CSF-ADA level of TBM and other groups of meningitis ($p < 0.0001$). This significantly high value of CSF-ADA had also been shown by various worker like, Rana SV et al., reported sensitivity of 66.6% and specificity of 90% at Cut-off value 10 IU/L [23], Kashyap RS et al., reported sensitivity of 82% and specificity of 83% at Cut-off value 11.39 IU/L [24], Choi SH et al., proposed a

cut-off value 15 IU/L with sensitivity 83% and specificity 95% [25], Chotmongkol V et al., reported sensitivity of 75% and specificity of 93% at cut-off value 15.5 IU/L [26], while Baro M et al., proposed low cut-off value of 6.5 IU/L with sensitivity of 83.3% and specificity of 85.3% [10], Gambhir IS et al., also proposed low cut-off value of 8 IU/L with sensitivity of 44% and specificity of 75% [27], and Baheti R et al., proposed cut-off value of 6.5 IU/L with sensitivity of 95.38% and specificity of 92.85% [28].

The age and sex distribution of TBM cases are shown in [Table/Fig-2,3]. The number of TBM cases increased in 15-24 years of age group (total no. 14) and decreased in 45 and above year of age group (total no 2). As regards to age, CSF activity in 15-24 year age group ranged from 8.6-28 IU/L with a mean of 12.97 IU/L. In 25-34 year age group its value ranged from 9.8 to 26.3 IU/L with a mean of 14.60 IU/L, and in age group 35-44 year its value ranged from 10.5 to 15.5 IU/L with a mean of 13 IU/L. No significant difference was noted in mean CSF-ADA activity with respect to age.

CSF-ADA activity in male ranged from 8.6 to 28.0 IU/L with mean of 13.4 IU/L and in female it ranged from 9.7 to 26.3 IU/L with mean of 13.73 IU/L; no significant difference was noted with respect to sex.

Pyogenic Meningitis

The 12 cases of PM, which consisted of 7 males and 5 females of different age were studied. The CSF-ADA value ranged from 4.2 to 10.4 IU/L with mean 7.68 IU/L and SD \pm 2.00 as shown in [Table/Fig-4]. All the cases showed higher than normal value. Comparative study with the TBM group showed p-value ($p < 0.0001$) which indicates the result to be significant. The CSF-ADA activity overlapped with TBM and AM however the mean value was much lower compared to TBM (13.73 IU/L). Similar observation were made by various workers like, Gambhir IS et al., observed low mean CSF-ADA value of 7.92 ± 0.95 IU/L in PM and 18.22 IU/L in TBM [27], Choi SH et al., found mean CSF-ADA value of 7.38 ± 3.27 IU/L in pyogenic meningitis and 12.76 ± 7.53 IU/L in TBM [25], Donald PR et al., found higher mean value than the present result in case of TBM [29]. Higher CSF-ADA value can be attributed to the increased lymphocyte count in CSF which contains high enzymatic activity Piras MA et al., showed that the enzymatic activity strongly correlates with type of cell in the absolute number of cells [30].

Aseptic Meningitis

CSF-ADA activity was studied in 12 cases of AM (7 male and 5 females). The CSF-ADA value ranged between 2.2-10.8 IU/L with a mean value of 6.72 IU/L and S.D. \pm 2.71. Comparative study with TBM cases showed that in only two cases of AM CSF-ADA value are above cut-off value 10 IU/L while rest are below. Testing the data with t-test gives p-value of < 0.0001 indicating it to be significant. Similar value was observed by Rana SV et al., [23] Choi SH et al. [25], Gambhir IS et al., [27], Malan C et al., [31]. The pyogenic meningitis cases showed overlapping values with AM where as TBM cases have CSF-ADA values always more than that of AM as is clear from [Table/Fig-4]. Thus CSF-ADA activity can differentiate between TBM-AM. At the same time it cannot differentiate AM from PM. Despite lymphocytic pleocytosis in AM and TBM, how the CSF-ADA activity differs in these two conditions is not clearly known, most possible explanation for this may be that

1. Viral inflammation does not alter permeability of blood brain barrier.
2. ADA level are highest in T-lymphocyte than B-lymphocyte and the release of ADA differ due to differing value of the cells in these two (Malan C et al.) [31].

SUMMARY AND CONCLUSION

Though demonstration of AFB in CSF, CSF culture, CSF cytochemistry are the gold standard for diagnosis of TBM, the CSF-ADA estimation is a cost effective and reliable means to establish a

diagnosis of TBM and to differentiate it from non-TBM using a cut-off value of 10 IU/L.

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