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Original Research Article

Raised Adenosine Deaminase in Cerebrospinal Fluid: A Diagnostic Marker of Tuberculous Meningitis

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ABSTRACT

Background: Tuberculous meningitis (TBM) is an important and common central nervous system (CNS) infection, particularly in developing countries with high mortality rate. More accurate and rapid diagnostic tests are necessary to prevent delays in specific treatment and to prevent sequelae. Objective of the study was using Adenosine Deaminase (ADA) levels in CSF as rapid screening tests to differentiate various types of meningitis.
Methods: The study was conducted in patients with signs and symptoms of meningitis of varied etiology. Diagnosis was made by appropriate and relevant investigations and patients were categorised in different groups, depending upon the accepted criteria. CSF-ADA estimation was done by spectrophotometer.
Results: According to the accepted criteria 30 patients (52%) having fulfilled the criteria were labeled as tubercular, while the other 28 (48%) were labeled as non-tubercular. Mean CSF ADA levels in tuberculous meningitis groups was significantly higher as compared to pyogenic meningitis and viral meningitis. Our study results indicate that ADA level estimation in CSF not only helps in the diagnosis of TBM, CSF ADA level 10U/L as a cutoff value exhibited 96.66% sensitivity, 100% specificity and 100% positive predictive value in differentiating tuberculous from non-tuberculous meningitis.
Conclusion: CSF-ADA level is a simple and reliable test in differentiating TBM from other types of meningitis.

Keywords: Tuberculous Meningitis, cerebrospinal Fluid, Adenosine Deaminase(ADA)

INTRODUCTION

Meningitis, which is inflammation of the protective membranes covering the brain and spinal cord, may be caused by infection with viruses, bacteria, mycobacterium tuberculosis, or other microorganisms and less commonly by certain drugs.

Tuberculous meningitis (TBM) is an important and common CNS infection, particularly in developing countries. [1] In these countries, TBM accounts for more than 20percent of community-acquired meningitis in adults. [2] TBM is associated with high rates of mortality and neurological disability, particularly in children and in immunocompromised patients. [3] More accurate and rapid diagnostic tests are necessary to prevent delays in specific treatment and to prevent sequelae. A positive mycobacterial culture in the cerebrospinal fluid (CSF) remains the gold standard in TBM diagnosis. CSF acid-fast bacilli are identified in less than 10% of

cases, and mycobacteria culture positivity ranges from 50% to 75% after 8 weeks, an unacceptable length of time for the diagnosis of tuberculosis. [4]

Despite the advantages of the automated mycobacteria culture systems, the mean recovery time remains too long for making treatment decisions. [5]

The characteristic CSF abnormalities in TBM are similar to those accompanying a variety of meningeal processes, such as partially treated bacterial meningitis, fungal meningitis, syphilitic meningitis, and vasculitis. Bacterial meningitis and TBM may have similar characteristics in developing countries and aseptic meningitis may also need to be ruled out. Thus, the decision to treat or not to treat a patient as a TBM patient is a relatively common one in clinical practice. Abnormalities include a moderate lymphocytic pleocytosis with moderately elevated spinal fluid protein and moderate hypoglycorrhachia. [1] Due to the difficulty of establishing the diagnosis of TBM using clinical, radiological (MRI or CT), biochemical, cytological and even microbiological approaches, additional tests have been developed. These include indirect and direct products from Mycobacterium tuberculosis, such as adenosine deaminase (ADA) activity, radioactive bromide partition test, tuberculostearic acid assay, antibodies against mycobacterial antigens and nucleic acid amplification reactions.

The use of ADA estimation is increasing as it is simple and cost effective. High ADA levels in tuberculosis appear to be related to the subset of activated T-lymphocytes in response to tuberculous antigens. [6] Nevertheless, several cut-offs for ADA in TBM have been proposed by different studies, and thus, there is a lack of standardization in the ADA cut-off value for diagnosing TBM. The sensitivity, specificity and positive and negative predictive values for ADA depend on the selected cut-off value, the control group and the local prevalence of tuberculosis. The reported sensitivity has varied from 40% to 100%, and the specificity from 70% to 100%. [7]

The goal of this study was to evaluate the CSF-ADA test as a diagnostic test for TBM.
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MATERIALS AND METHODS

A total of 58 clinically suspected cases of meningitis, admitted in Burdwan Medical College & Hospital, Burdwan were studied. All the cases were examined clinically and their CSF and blood samples were collected for various investigations after taking proper written consent.

Of the selected 58 cases, 30 cases were of tuberculous meningitis, 8 cases of pyogenic meningitis and 20 cases of aseptic meningitis.

Lumbar puncture was done in each case and at least 2 ml of CSF was collected in a sterile vial and subjected to biochemical and microscopic examination. The valid set of criteria, as used by Ahuja et al [8] was used to categorize tuberculous meningitis patients. The criteria were as follows:

A) Clinical features:

- Fever and headache more than 14 days (mandatory)
- Vomiting, alteration of sensorium, focal deficits (optional).

B) CSF showing:

- Pleocytosis with more than 20 cells
- More than 60% lymphocytes
- Sugar less than 60 percent of corresponding blood sugar
- Negative Indian ink preparation studies
- Malignant cytology (when relevant)

C) CT showing one or more of

- Exudates in basal cistern
- Hydrocephalus
- Infarcts
- Gyral enhancement

D) Active extraneural tuberculosis as evidenced by appropriate

- Radiological tests
- Microbiological tests or
- Cessation necrosis on histopathological examination.

Based on the above criteria the following classification was made:

1. Highly probable .....A + all of B, C, D
2. Probable.....A + any 2 of B, C, D
3. Possible.....A + any 1 of B, C, D

Diagnostic criteria of pyogenic meningitis: The typical CSF findings were elevated pressure, neutrophilic pleocytosis, i.e. cell count >100 WBC/cu.mm consisting of more than 90% polymorphs, elevated protein >40 mg%, sugar ≤50 % of the blood sugar ,cloudy or turbid appearance, culture and gram staining may be positive for bacteria.

Diagnostic criteria of Aseptic meningitis: The typical findings were: sugar ≤2/3 of blood sugar, proteins ≤40 mg %, cell count > 100 WBC/cu.mm and consisted predominantly of lymphocytes.

CSF-ADA activity was estimated in all fifty-eight cases spectrophotometrically by Guisti [9] method and comparison was made between the levels in tuberculous meningitis, pyogenic meningitis, and aseptic meningitis.

Reagent used: MICROEXPRESS-ADA-MTB (TULIP Diagnostics Pvt. Ltd.)

Statistical analysis was performed by SPSS (version 11.5) software for calculation of mean, standard deviation, sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of CSF ADA level.

RESULT

According to the accepted criteria 30 patients (52%) having fulfilled the criteria were labeled as tubercular, while the other 28 (48%) were labeled as non-tubercular.

In our study, the commonest symptoms (94%) were fever, which was usually low grade, lasting for more than 2 weeks associated with headache generalized, continuous, increasing on cough and sneezing. Altered sensorium (80%) was the next common symptom. Of them the most common was drowsiness (53.33%), cranial nerve involvement seen in 53.33% of cases. 6th nerve palsy is the commonest followed by 2nd, 7th nerves Hemiparesis is observed in 6.66 percent cases. Signs of meningeal irritation are almost universally present.

According to Ahuja et al clinical criteria, in the present study, there were two highly probable, eight probable and 20 possible cases of tuberculous meningitis.

Mean CSF ADA levels in tuberculous meningitis groups was significantly higher as compared to pyogenic meningitis and viral meningitis (Table 1,Figure 1).

Table 1 : CSF ADA value in different groups

ADA (P< 0.05)	TUBERCULAR MENINGITIS	BACTERIAL MENINGITIS	VIRAL MENINGITIS
No. of cases	30	8	20
Mean	15.0567	6.6875	4.6710
Median	14.6500	6.6500	4.9500
Std. Deviation	4.91666	1.28668	1.03577
Minimum	9.20	4.60	2.80
Maximum	36.50	8.40	6.10

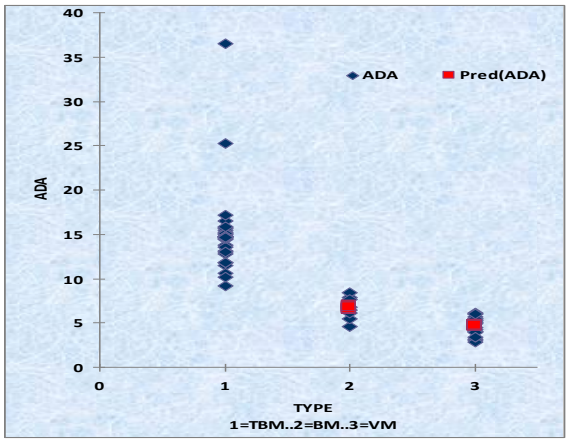

Figure-1: CSF ADA value in different groups

There was no correlation between CSF sugar levels with ADA (Table 2).

Table-2: CSF ADA levels in TB meningitis in relation to CSF sugar

CSF sugar (mg%)	No. of cases	CSF ADA Levels (U/L)		
		Mean	SD	Range
Less than 40	25	15.29	1.97	9.2-36
More than 40	5	13.7	2.05	11.-18.50

There was direct correlation between CSF protein and ADA levels (Table 3).

Table-3: CSF ADA levels in TB meningitis in relation to CSF proteins

CSF PROTEIN (mg%) (p < 0.05)	TOTAL NO. OF CASES	ADA LEVEL (U/L)		
		MEAN	STD. DEVIATION	RANGE
0 - 100	8	11.9	1.15	10.20-13.50
101 - 200	11	14.11	1.76	9.20–15.70
> 200	11	18.29	6.75	14.40-36.50

Direct correlation was found between the CSF lymphocyte count and ADA levels (Table 4)

Table-4: CSF ADA levels in TB meningitis in relation to CSF lymphocyte Count

CSF CELL (count/ cumm) (p < 0.05)	TOTAL NO. OF CASES	ADA LEVEL (U/L)		
		MEAN	STD. DEVIATION	RANGE
0 - 50	3	10.76	0.66	10.20 – 11.50
51 - 70	5	12.58	0.75	11.80 – 13.50
71 - 90	12	16.22	6.65	9.20 – 36.50
> 90	10	16.18	3.26	14.40 – 25.20

CSF-ADA level 10 IU/L as a cut-off value test exhibited 96.66% sensitivity, 100% specificity and 100% positive predictive value in differentiating tuberculous from non-tuberculous meningitis

DISCUSSION

There is always an emergency in diagnosing tuberculosis correctly in patients with meningitis because specific treatment is most effective when started early in the course of illness. Irreversible brain damage may occur while awaiting for culture report for confirmed diagnosis. In the present study, diagnosed cases of tuberculous meningitis were studied in details and diagnostic ability of ADA was evaluated in comparison with pyogenic and viral meningitis.

The peak incidence of TBM in the present study was found in young adults in the age group of 21-30 years (46.67%). It is similar to Virmani et al [10] who observed 35.5% in their study.

According to the present study, the incidence of TBM in males was 60% and in females 40%. The incidence in both males and females is consistent with the study done by Gambhir et al. [11]

In the present study, history of fever is present in majority of the cases of TBM (93.33%). It is low-grade, more in the evening, associated with night sweats. In Khatua et al [12] study the incidence of fever was 87%, while it was 58.9% in the study carried out by Virmani et al. [10]

In the present study, there are two highly probable cases, eight probable cases and twenty possible cases of tuberculous meningitis. This is almost consistent with Gambhir et al [11] study, but there were no cases in highly probable group in that study.

Mean CSF ADA level was significantly higher in TBM patients (15.056) as compared to pyogenic meningitis (6.687), viral meningitis (4.671). In Gambhir et al [11] study, mean CSF ADA level in TBM patients was 9.61±4.10 U/L and was significantly elevated as compared to viral encephalitis and enteric encephalopathy cases. In Prasad et al [13] study, the mean CSF ADA levels were 6.43±1.93; 1.89±0.91; 0.90±0.45 and 0.64±0.57 U/l in tuberculous meningitis, pyogenic meningitis, aseptic meningitis and controls respectively. Mishra OP et al [14] found that mean CSF-ADA level was significantly raised in TBM as compared to partially treated bacterial meningitis patients. The CSF ADA values in pyogenic meningitis cases are intermediate to the respective values of Gambhir et al [11] and Prasad et al. [13] In the aseptic meningitis group, the values of ADA are higher as compared with the respective values in Prasad et al, [13] but not in the range of tuberculous meningitis group, as well as ADA levels in control groups of the present study were higher when compared to the values of Prasad et al. [13]

The ADA values in tuberculous meningitis group in the present study when

compared with the ADA levels in other groups such as pyogenic meningitis, viral meningitis, the p-value was <0.001 and was statistically significant.

CSF protein levels were raised in all the cases of TBM. When the protein levels were compared with CSF-ADA levels, there was significant correlation between CSF ADA levels and CSF protein levels. These findings were consistent with the findings of Prasad et al [13] study and Gambhir et al [11] study.

CSF lymphocyte counts were raised in all the cases. There was a definitive correlation between the CSF ADA values and lymphocyte count. This is simple to explain as the adenosine enzyme is required for T-lymphocyte proliferation and differentiation. The findings of the present study were consistent with Prasad et al [13] and Gambhir et al [11] studies.

CONCLUSION

This study was done to evaluate the diagnostic utility of CSF-ADA activity in tuberculous meningitis. The mean CSF ADA value in tuberculous meningitis was statistically significant (p<0.001) when compared to the CSF ADA values in pyogenic meningitis and viral meningitis.

In conclusion, ADA estimation in CSF is not only simple, cost-effective, rapid and reliable but also a useful differential diagnostic marker of TBM, especially when there is a confusion of differentiating the tuberculous etiology from non-tuberculous. As CSF ADA estimation in TBM can be easily made available and performed with minimal training, this may find a place as a routine investigation.

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