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IJPBS |Volume 4| Issue 1 |JAN-MAR|2014|95-98

Research Article
Biological Sciences

CEREBROSPINAL FLUID–ADENOSINE DEAMINASE ATIVITY IN TUBERCULOUS MENINGITIS CASES

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ABSTRACT

Context: *Tuberculosis remains one of the world's deadliest diseases & tubercular meningitis is one of the most deadly complications due to missed diagnosis and delayed Treatment and result in significant morbidity and mortality. The signs and symptoms, results of routine analysis of CSF and radiographic findings for patients with CNS tuberculosis are often inadequate in making a definitive diagnosis.* ***Aims:*** *1. To study the levels of Adenosine deaminase in CSF in cases of meningitis. 2. To evaluate the sensitivity and specificity of CSF-ADA as a diagnostic test in tuberculosis meningitis.* ***Material and methods:*** *In the cross sectional study, Adenosine deaminase activity (ADA) was studied in cerebrospinal fluid of 25 cases of tuberculous meningitis, 10 cases of pyogenic meningitis. 21 cases of aseptic meningitis and10 control subjects.* ***Results:*** *The mean CSF-ADA activity was 16.324±0.706 (tuberculous meningitis); 8.89±1.03 5.01±0.68 (pyogenic meningitis); 8.89±1.03 (aseptic meningitis) and 2.15±0.51 IU/L (control) respectively. The sensitivity and specificity of this test for diagnosis of tuberculous meningitis was 94.73% and 90.47% respectively with ADA value of more than 10 U/L.* ***Conclusion:*** *The adenosine deaminase levels in tuberculous meningitis cases was statistically significant. It can play a major role towards early diagnosis of tuberculous meningitis and help in treatment to prevent from fatal and morbid complications of tubercular meningitis.*

KEY WORDS

Tuberculous meningitis; Cerebrospinal fluid; Adenosine deaminase

INTRODUCTION

Tuberculosis is one of the oldest and commonest infectious diseases which occurs in all age groups and both sexes and is known as the captain of death. Tuberculosis usually affects lung but extra pulmonary tuberculosis is also common, of which meningeal tuberculosis is the most hazardous.CNS tuberculosis is occurs in 2-5% of all patients with tuberculosis and in 10% of those with AIDS-related tuberculosis and is associated with high mortality rate and serious neurological complications.[1].Tuberculous meningitis (TBM) remains a serious clinical problem and in 50% of cases, there exists concurrent non neuro tuberculosis. The signs and symptoms,routine CSF analysis and radiography for patients with TBM often do not suffice inarriving at a definitive diagnosis. A laboratory confirmation becomes essential. The most rapid but an insensitive method of detecting mycobacteria is the acid fast staining of deposit of centrifuged specimen of CSF.The gold standard method of diagnosis, isolation of Mycobacterium tuberculosis from CSF samples, is timeconsumingand the result also depends on the volume of CSF used for culture.[2] The polymerase chain reaction (PCR) to detect Mycobacterium tuberculosis specific DNA is next alternative for a definitive diagnosis; however, the infrastructure required for facilities to perform the test are expensive and the test is not affordable because of its high cost. ADA is an enzyme catalyzing the deamination reaction from adenosine to inosine. It is also an essential enzyme of the purine catabolic pathway. ADAis present in all cell types; however, the

amount of enzyme differs widely among tissues. The highest ADA levels in humans are found in lymphoid tissues.[3] Detection of high level of ADA has been used in the diagnosis of tuberculous pleural, peritoneal and pericardial effusions.[4,5]. This study was designed to study the levels of ADA in cases of meningitis.

MATERIAL & METHODS

This cross sectional study was done in the central diagnostic laboratory of our teaching hospital from January 2012 to December 2013**.** Adenosine deaminase activity (ADA) was studied in cerebrospinal fluid (CSF) of 56 cases of meningitis. ADA was also studied in 10 controls, who were, patients without any neurological disorders. The CSF specimen was collected in the controls while doing lumbar puncture for spinal anaesthesia. Newly diagnosed cases of meningitis only was included in the study. Cases of meningitis like clinical picture, due to other causes like head injury, history of fall and cerebral malaria were excluded.

Cases with a clinical diagnosis of meningitis, admitted in our teaching hospital, which is a tertiary care centre, were selected. A thorough clinical examination was done, followed by routine blood investigations and CSF analysis (microbiological, biochemical and cellular). In addition, CSF-AD Aactivity was estimated by immune turbidimetric analysis using ADA-MTB kit (Microexpress, Tulip Co). The data was analysed by One way ANOVA test using the Origin® 6.0 (Microcal software, Inc. USA)

RESULTS

During the study period we enrolled, a total of 56 newly diagnosed cases of meningitis. CSF analysis in these patients categorized 10 as pyogenic meningitis, 21 as aseptic meningitis and 25 cases as tubercular meningitis. CSF-ADA level was estimated and compared. CSF –ADA levels were higher in tubercular meningitis cases compared to the normal cases. ADA activity was also found high in pyogenic as well as aseptic meningitis; though not as high as in tubercular meningitis. The cut –off was taken as 10 IU/ml as per the literature of the kit manufacturer.22 patients of tuberculous meningitis had > 10 IU/ml, 3 patients of pyogenic meningitis and 2 of aseptic meningitis had values > 10 IU/ml. The mean ADA in tuberculous cases was 16.324±0.706 and in that of pyogenic and aseptic was 8.89±1.03 and5.01±0.68.

DISCUSSION

Demonstration of tubercle bacilli in CSF by microscopy and culture remains the gold standard method for diagnosing tuberculous meningitis but in most cases direct smears are negative and cultures of CSF is usually difficult .[6] Recent methods such as those involving bacterial DNA amplification by PCR or other similar methods, are expensive and not available for widespread use. Routine CSF laboratory findings do not help diagnose TBM with a good accuracy. A simple and rapid test that can help to differentiate it from other causes and hence diagnose TBM indirectly is always necessary.

ADA has a major role in proliferation and differentiation of T lymphocytes. It also acts in maturation of monocytes and transforming them to macrophages. ADA is a significant indicator of active cellular immunity. Cell-mediated immunity plays an important role in tuberculosis infection. ADA activity in serum has been studied in pulmonary and serosal tuberculosis and it has been proposed to be a useful surrogate marker for TB because it can be detected in body fluids such as pleural, pericardial and peritoneal fluid.[7] The levels of ADA increase in TB because of the stimulation of T cells by mycobacterial antigens.

In our study, CSF –ADA levels were higher in tubercular meningitis cases compared to the non tuberculous meningitis and in normal cases. 22 patients of tuberculous meningitis had > 10 IU/ml and 3 patients had values just less than the cut-off. 3 patients of pyogenic meningitis and 2 of aseptic meningitis had values > 10 IU/ml but < 14 IU/ml. The CSF- ADA levels in tuberculous cases were 16.324±0.706 and in that of pyogenic and aseptic was 8.89±1.03 and5.01±0.68. (**Table 1**).

Table1: CSF-ADA levels in different types of meningitis.

GROUP	No. of cases	CSF-ADA Mean(IU/L)	Min	Max	Variance
Tuberculous meningitis	25	16.324	11.4	23.2	12.4744
Pyogenic meningitis	10	8.89	3.5	13.7	10.71656
Aseptic meningitis	21	5.0095	2.1	13.6	9.9319
Controls	10	2.15	0.6	5.1	2.605
F = 71.28633					
p = 0					
At the 0.05 level, the means are significantly different.					

3 cases of bacterial meningitis 2 cases of aseptic meningitis had ADA level just above the cut-Off. This is possibly because ADA value in most assays detects total ADA which includes ADA-1 and ADA-2. Thus, fluid with high cell counts (e.g. bacterial meningitis) can have high total ADA and may occasionally be difficult to differentiate from tuberculous meningitis.

Several studies have reported the usefulness of CSF-ADA in diagnosing TBM, differentiating it from other forms of meningitis. [8,9,10,11] In our study, statistically significant difference in the CSF - ADA levels of meningitis due to tuberculosis and non-tuberculous etiology ($P < 0.05$) was observed. Results of our study indicate that ADA levels in CSF are of substantial value in diagnosis of TBM and in differentiating this disease from others. ADA level in CSF showed a sensitivity of 94.73% and specificity of 90.47% for the diagnosis of tuberculous meningitis. When it is difficult to establish the etiology by specific tests for tuberculous meningitis, CSF – ADA levels help make a decision towards diagnosis and hence treatment may be initiated.

A study using 10 U/L as cutoff value for diagnosis of TBM, reported sensitivity 66.6% and specificity as 90% .[12] Another investigator found that CSF ADA may differentiate tuberculous from non-tuberculous meningitis even at a cut-off level of 6.5 U/L .[13]

CONCLUSION

The mean CSF-ADA value in tuberculous meningitis was statistically significant ($p<0.05$) when compared to the CSF-ADA values in non tuberculous meningitis and controls. CSF-ADA estimation in tuberculous meningitis has a sensitivity of 94.73% and specificity of 90.47% in the present study. ADA activity in CSF is a of great value in the early diagnosis of tuberculous meningitis.

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