

Diagnostic Efficacy of Adenosine Deaminase Levels in CSF of Children With Tuberculous Meningitis

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ABSTRACT

Background: Tubercular Meningitis (TBM) is a common form of Bacterial Meningitis caused by Mycobacterium Tuberculosis. The diagnosis of TBM is often difficult and confusing. Diagnostic method which is easy, simple, cost effective and easily available can be of great help.

Aim: The aim of this study is to assess Diagnostic efficacy of adenosine Deaminase (ADA) levels in CSF of children with Tuberculous Meningitis.

Materials and Methods: A total of 60 patients were evaluated for the study. Out of 60 cases, 25 cases were diagnosed as Tuberculous Meningitis based on clinical data, history, CSF findings and subsequent course. The ADA activity in CSF of these 25 cases was measured and analyzed by the method of Giusti.

Results: Tuberculous meningitis was diagnosed in 25 out of 60 cases, clinically and by CSF examination. Mean level of ADA in CSF in tuberculous meningitis patients was found to be 16.81 ± 6.063 . Among 25 cases of tuberculous meningitis, one showed low ADA level (4.10 U/L). The sensitivity of ADA test in CSF is determined at a cut off level of 10 U/L.

Conclusion: Adenosine deaminase activity in CSF is a relatively inexpensive and easy procedure. It can be of great value in the diagnosis of tuberculous meningitis. It can be performed in any laboratory.

Key words: Tuberculous Meningitis, Cerebrospinal Fluid, Adenosine Deaminase Activity.


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INTRODUCTION

Tuberculous meningitis is a dangerous complication of infection caused by Mycobacterium tuberculosis and it is one of the leading causes of mortality and morbidity in developing countries. Tuberculous meningitis is considered as one of the most dangerous extra pulmonary disease which accounts for 7-12% of tuberculosis cases in developing country.¹ According to WHO, approximately 16 million people are suffering from active tuberculosis with an estimated 8.5 million developing active tuberculosis every year, which results in approximately 2 million deaths.²

Diagnosis of tubercular meningitis remains a matter of concern due to unspecific nature of the disease. Various diagnostic aids used are bacteriological method, clinical, radiographical method etc. Diagnostic test which is easy, reliable, cost effect and helps in detection of acid fast bacillus is of great value. According to available literature tuberculosis infection can be detected by non-cultural methods such as latex agglutination, radioimmuno-assay, and enzyme linked immunosorbent assay, however these techniques lack sensitivity and specificity.³⁻⁵ In this context the

pressing need for an additional biochemical test which is simple to perform, inexpensive and of considerable help in diagnosis of tuberculous meningitis has been felt since long time.

Adenosine deaminase is an enzyme involved in purine catabolism which is widely distributed in mammalian tissue, especially in lymphoid tissue. ADA catalyzes the deamination of adenosine, forming inosine in the process.⁶ ADA activity is found to be high in T lymphocytes and macrophages. Lymphocytes and macrophages release ADA during cellular immune response. The present study was conducted to assess Diagnostic efficacy of adenosine Deaminase levels in CSF of children with tuberculous meningitis.

MATERIALS AND METHODS

The study was carried out in the Department of Pediatrics, with the help of Department of Pathology of Vivekananda Polyclinic & Institute of Medical Sciences, Lucknow for a period of 1 year. A total of 60 patients were evaluated for the study. Out of 60 cases, 25 cases were diagnosed as tuberculous meningitis based on

clinical data, history, CSF findings and subsequent course. Age group selected for the study was 1 month to 14 years. Ethical committee clearance was obtained before beginning the examining patients. Patients/Guardians were explained about the study. A written informed consent was obtained from patient's guardian before including in the study. All the patients were examined; a detailed case history was obtained regarding age, sex, past history of tuberculosis, any contact with tuberculosis patients etc. Inclusion and exclusion criteria were as follows:

Inclusion Criteria

1. Children admitted in Pediatric ward / Pediatric ICU of Vivekananda Polyclinic & Institute of Medical Sciences with tuberculous meningitis.
2. Patients age ranges between one month to fourteen years.

Exclusion Criteria

1. Age less than one month & more than fourteen years
2. Patients with history of previous CNS illness.

The ADA activity in CSF was measured by the method of Giusti in all 25 patients.⁷ It was assayed by measuring the ammonia formed during the 60 minutes of incubation. Ammonia reacts in presence of sodium nitroprusside as a catalyst with sodium hypochlorite and phenol, in alkaline solution, producing a deep blue indophenol. The ammonia concentration is directly proportional to the absorbance of the indophenol. CSF cell count was measured for all the patients.

Data Analysis: Data collected was tabulated and subjected to analysis using Statistical Package for Social Sciences (SPSS) Version 15.0. Non parametric data has been represented as frequencies and percentages.

Table 1: CSF ADA levels vs. CSF cell count in TBM cases n=25

CSF Cell Count/cu. mm.	No. of cases	Mean ADA levels U/L
<200 Cells	10	15.41±3.30
>200 Cells	15	17.75±7.33

Table 2: CSF ADA levels – CSF protein in TBM cases

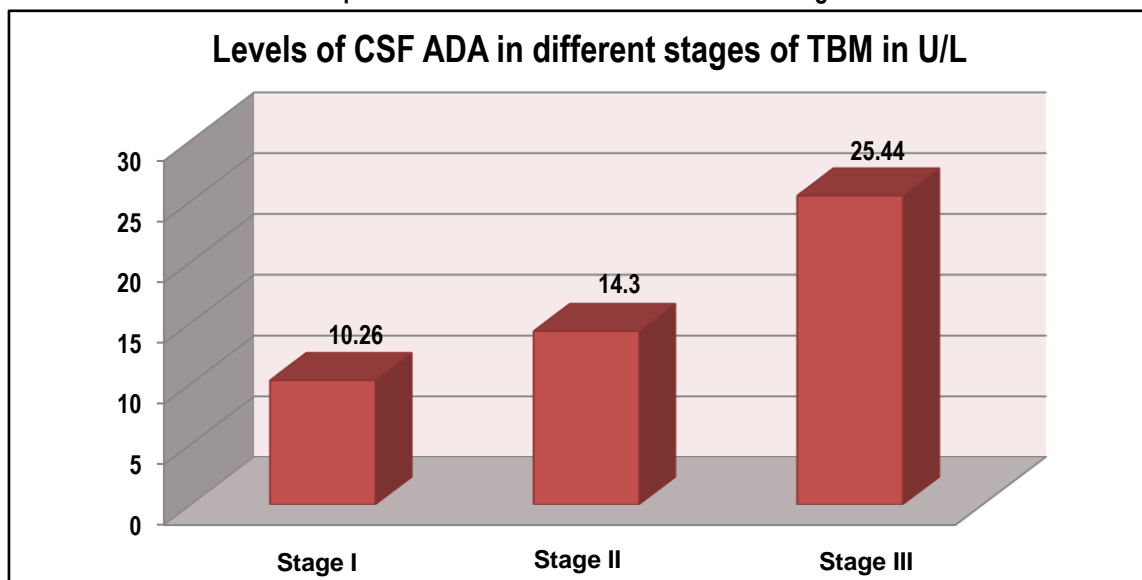
CSF Protein	No. of cases	Mean ADA levels U/L
40 – 100 mg	10	17.09±6.79
More than 100 mg	15	16.63±5.77

Table 3: CSF ADA levels in relation to clinical stage of the disease

Stage of tuberculous meningitis	No. of Cases	Mean levels of CSF ADA U/L
Stage I	1	10.26
Stage II	18	14.30±3.582
Stage III	6	25.44±3.512

$$\chi^2=23.682; p<0.001$$

Graph 1: Level of CSF ADA in tuberculous meningitis



RESULTS

60 cases of CNS infection and suspected CNS infection were evaluated during the period, May 2008 to May 2009. Out of 60 cases, clinically and by CSF examination, tuberculous meningitis was diagnosed in 25 cases. Patients selected for the study were aged between 1 month and 14 years. Out of 25 cases, 14 were males and 11 females. 72 % of cases of TBM were under the age of 5 years and most were in the age group of 2-5 year accounting for 52 %.

CSF cell count was found to be <200 Cells in 10 cases and mean ADA level was 15.41±3.30. In 15 cases CSF cell count was >200 Cells and ADA level was 17.75±7.33 (Table1). There was no significant difference found between CSF ADA activity in relation to cell count ($p=0.355$). CSF protein levels were compared with ADA levels. CSF protein was found between 40-100 mg/dl in 10 cases (ADA level 17.09±6.79) whereas in 15 cases, CSF protein was more than 100 mg/dl (ADA level 16.63±5.77). No correlation

was found between CSF protein and CSF ADA levels (Table 2). Mean level of CSF ADA in CSF of patients with TBM was found to be 16.81 ± 6.063 . In 25 cases of tuberculous meningitis, one showed low ADA level (4.10 U/L). The sensitivity of ADA test in CSF is determined at a cut off level of 10 U/L.

Out of 25 cases, 1 case was reported to be in stage 1. 18 cases were found to be in stage 2 while 6 cases were reported to be in stage 3. CSF ADA level was found to be 25.44 ± 3.512 in stage 3 (Table 3). p value was found to be $p < 0.001$. There was little difference between stage I and stage II. But in stage III cases, ADA activity was significantly higher than other two stage groups (Graph 1).

DISCUSSION

Adenosine deaminase has been used as a diagnostic aid in other diseases like Liver disease e.g. cirrhosis, Tuberculosis, Brucellosis, Infectious Mononucleosis, Viral Hepatitis and HIV. Hankiewicz J and Lesniak reported that Levels of Adenosine deaminase (ADA) in CSF are known to be raised in tuberculous meningitis.⁸ In present study the level of ADA in CSF of tubercular meningitis patient was found to be high. Piras and Gakis suggested that ADA levels in CSF may help to differentiate tuberculous meningitis from viral meningitis and further that tuberculous meningitis and pyogenic meningitis differ clearly from one another.⁹ However cases of viral and pyogenic meningitis were not included in our study.

Kashyap et al. found CSF ADA activity significantly higher in CSF of TBM patients, 14.31 ± 3.87 (2.99–26.94), than in the CSF from non-TBM infectious meningitis, 9.25 ± 2.14 (4.99–13.96).¹⁰ In our study the mean level of ADA in CSF in tuberculous meningitis patients was found to be 16.81 ± 6.063 which was higher than those reported by others. Ribera et al.¹¹ reported elevated ADA activity in the CSF of patients with bacterial meningitis which had high cell counts whereas in our study there was no significant difference found between CSF ADA activity in relation to cell count ($p = 0.355$). Malan et al. suggested that the level of this enzyme in CSF is useful in distinguishing TBM from bacterial meningitis.¹²

In present study the sensitivity of ADA level in CSF was determined at a cut off of 10 U/L. OP Mishra et al. suggested a cut off CSF ADA level of > 5 IU/L for the diagnosis of tubercular meningitis whereas Gambhir et al. reported a cut off value 8 IU/L/min, and overlap between TBM and non-TBM patients were seen, especially for infectious neurological disorders like pyogenic meningitis.^{13,14} M.Y. Rohani conducted a study on diagnostic value of adenosine deaminase (ADA) activity and its use in the differential diagnosis of tuberculous meningitis. They concluded that ADA was not specific enough to be used as a rapid diagnostic test, however results in our study are in contrast with those reported by others.¹⁵

CONCLUSION

ADA estimation in the CSF is simple, inexpensive and a rapid method in early diagnosis of tuberculous meningitis. This test can be used as a routine diagnostic procedure in tuberculous meningitis patients. It can be performed in any laboratory, no special instruments are required. Its ability to differentiate other forms of meningitis was not evaluated in our study and larger studies are needed to comment on this aspect.

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