ROLE OF CEREBROSPINAL FLUID ADENOSINE DEAMINASE IN DIAGNOSIS OF TUBERCULAR MENINGITIS IN ADULTS

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ABSTRACT

BACKGROUND

Tuberculous meningitis (TBM) still remains an important cause of morbidity and mortality in India. Due to lack of early and timely diagnosis of TBM, the fatality rate remains high.

OBJECTIVES

To evaluate the role of Adenosine Deaminase (ADA) activity in the Cerebrospinal Fluid (CSF) in diagnosis of Tubercular meningitis in adults.

MATERIAL AND METHODS

The study included 100 patients who presented with sign and symptoms suggestive of meningitis. All the patients were admitted; detailed history and examination including neurological examination was done. CSF samples were taken along with other routine investigations. CSF analysis was done for sugar, protein, cells, and ADA. X-Ray Chest was done in all patients to find out the lung involvement.

RESULTS

Out of a total of 100 patients, 49 were diagnosed as TBM based on the clinical features and CSF analysis. The CSF showed pleocytosis of 10 to 500 cells/mm3 predominantly lymphocytes, protein >45mg/dl, sugar<40mg/dl or <40% of blood glucose concentration. The mean ADA activity was 12.54±3.91 U/L in patients with TBM. The sensitivity and specificity was 75.51% and 100% respectively when a cut-off value of ADA of 10U/l was used, with an accuracy of 88%.

CONCLUSIONS

ADA activity in the CSF is very important and rapid screening test that can help in the diagnosis of TBM. ADA activity is markedly higher in TBM.

KEYWORDS

Adenosine Deaminase (ADA); Meningitis; Cerebrospinal Fluid (CSF).

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INTRODUCTION: Tubercular Meningitis is an important cause of morbidity and mortality in India. There is a lack of early and timely diagnosis of TBM leading to high fatality rate.[1] Even when in some patients it is not fatal, the sequelae are concerning and disabling. Hence, there is a requirement of early and correct treatment for a successful outcome in patients of TBM.[1]

Meninges are the protective membranes which cover the brain and spinal cord, inflammation in these membranes is called meningitis.[2]

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The cause of inflammation is an infection of the fluid surrounding the brain and spinal cord.[2]Early and proper diagnoses of meningitis and adequate management is the key to lessen mortality and disability due to the disease.[3]

Study of CSF using gram stain smears provide a reliable and accurate method of diagnosis of Meningitis in 60%–90% of patients; concentration of bacteria in CSF correlate with percentage.[4]

Reliable, cost effective, rapid screening tests like ADA activity in CSF could serve in the differentiation of various types of meningitis in adults. High ADA would make the diagnosis of TBM more convincing.[5]

ADA is an enzyme of purine salvage pathway that catalyses the hydrolytic deamination of adenosine to inosine and ammonia. ADA in the CSF can be a sensitive and specific target for the diagnosis of TBM.[6]

This prospective study was designed to assess the significance of using ADA activity in CSF as rapid screening tests for the diagnosis of TBM.

MATERIALS AND METHODS: A total of 100 patients of who presented with clinical presentation suggestive of Meningitis were included in the study. All the patients were admitted in the Department of Medicine and Neurology, GR Medical College, Gwalior (MP).

All patients were above 18 years of age with clinical features suggestive of meningitis. Exclusion Criteria were patients with age less than 18 years, acute infections at sites other than the central nervous system, those in whom lumbar puncture was contraindicated, and patients with severe hepatic dysfunction, using contraceptives and steroids and those with who were found to have Meningitis other than TBM.

Patients with clinical features consistent with TBM like insidious onset of symptoms of meningitis, signs of meningeal irritation and presence of focal neurological deficits were included in the study. All patients underwent routine investigations including chest X-Ray for Lung involvement. The CSF samples of all patients were taken and analyzed for cell count, biochemistry (sugar & proteins) and ADA. ADA activity in CSF was determined in the pathology lab using ADA Kit. All the patients underwent CT scans of brain.

Patients were admitted and started with Symptomatic and supportive treatment till the diagnosis is confirmed. As soon as the CSF reports are available patients were started anti-tubercular treatment.

RESULTS: This was a prospective clinical study to evaluate the predictive value of ADA in TBM.

Out of 100 patients, on the basis of clinical presentation, CSF analysis and neuroimaging findings 49 patients were found to have TBM.

The majority (40%) of patients was within the age group of 21-40 years and 59% were males.

The clinical presentation of patients showed fever (95%) was the most common complaint followed by headache (83%). Other presentations were vomiting (52%), altered sensorium (45%), seizures (16%), drowsiness (8%), focal neurological deficits (9%), stupor (5%) and coma (4%).

CSF analysis of TBM patients showed pleocytosis of 10 to 500 cells/mm3 predominantly lymphocytes, proteins>45mg/dl, sugar<40mg/dl or <40% of blood glucose concentration. X-Ray of chest showed pulmonary infiltrations in 27 patients. CT scan brain showed evidence of meningeal enhancement, basal exudates or tuberculoma.

ADA activity in CSF was high in all the 49 TBM patients (mean value 12.54±3.91 IU/l). The cut-off value of ADA >10IU/L was considered high.

CSF cell count (cells/mm^3)	No. of cases (%)	CSF ADA(U/L) (mean±SD)
0-100	10	9.75±2.19
101-200	28	12.115±2.75
>200	11	16.99±4.9

Table 1: Relationship between CSF cell counts with CSF ADA in TBM

CSF; Cerebrospinal Fluid, ADA; Adenosine Deaminase.

CSF Protein (mg/dl)	No of cases	CSF ADA(U/L) (mean±SD)
0-100	23	11.05±1.98
101-200	21	13.50±4.31
>200	5	16.04±6.28

Table 2: Relation between CSF proteins in CSF ADA in TBM

At CSF ADA levels of>10 IU/L, the sensitivity and specificity of ADA with respect to TBM was 75.51% and 100% respectively with an accuracy of 88%. This value was statistically significant with p<0.0001.

DISCUSSION: We cannot deny that infectious diseases remain a major cause of death and disability for large number of people around the world despite regular progress in their treatment and prevention.[5] Infection in CNS can cause devastating abnormalities as vital tissues are involved and in some cases may result in to neurological and medical emergencies.

Meningitis has been reported to be common in males and young adults as was found in our study, which is similar to Kumar R. and Anderson NE, et al.[7,8]

The sign and symptoms of TBM are insidious in onset and include fever, headache, vomiting, drowsiness, stupor and coma. Our findings are similar to previous workers.[9]

The differential diagnosis of meningitis mainly depends on CSF analysis. In the present study CSF showed higher proteins, low sugars and raised cell count mainly lymphocytes. Nicolette N. B., et al has reported the similar findings. Our findings are consistent with them.[10]

Due to the lack of sureness in the currently available laboratory tests, the initiation of treatment of suspected cases of meningitis can often be delayed.[11] The specific screening tests which are reliable, cost effective and rapid and that can be performed in standard pathology laboratory could be very helpful in differentiating different types of meningitis in adults.[11]

For the definitive diagnosis of TBM, presence of Tubercle Bacilli either by smear and/or culture is the most commonly used laboratory method in present time.[11]

However, direct smear methods often show negative results in CSF samples and culturing of Mycobacterium Tuberculosis (MTB) takes 4-6 weeks to show the growth. Newer methods which involve amplification of bacterial DNA by the PCR method are not completely evaluated. Hence, despite extensive work on TBM, only few tests are available for diagnosis.[11]

Therefore, there is a need of a rapid test that could be beneficial in the diagnosis of TBM. Since early diagnosis and treatment of TBM can modify the outcome of patients, ADA seems to be the appropriate test for this purpose.

Studies have shown that CSF ADA activity is high in TBM and estimation of ADA level has been suggested to help differentiate TBM from viral and Bacterial Meningitis.[12]

Malan C, et al showed that mean ADA level in the CSF was significantly higher in TBM patients ($p<0.001$).[13] All the TBM patients in our study had higher ADA activity (mean 12.54±3.91 IU/l).

All the patients were started on anti tubercular therapy along with symptomatic and supportive treatment. In follow up period all patients recovered without any significant neurological sequel.

CONCLUSION: Early Diagnosis & treatment can bring down the mortality & morbidity of patients with meningitis. For patients presenting with unexplained fever, headache, nausea/vomiting, a spinal tap with blood cultures is indicated, if patients CT scan of brain is normal. In addition to routine CSF analysis (cell count, cell type, protein and sugar), ADA estimation can be done which is simple, inexpensive and the results are available fast. Thus, ADA levels in CSF can be used as good screening tool for the differential diagnosis of TBM. However, small number of patients is the limitation of our study, hence further studies with large number of patients are needed.

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