Diagnostic Role of CSF-ADA in Differential Diagnosis of Meningitis

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ABSTRACT

Introduction: Among the patients with meningitis, tubercular meningitis is an important cause of morbidity and mortality in India and other developing countries. Due to lack of early diagnosis, fatality is high in positive cases and sequel of disease may be distressing and disabling in the non-fatal cases. The estimated mortality due to tubercular meningitis in India is 1.5/100,000 population.Many literature has shown that CSF- ADA levels can differentiate various types of meningitis. Aim of the present study was to evaluate whether ADA levels can be used to differentiate various types of meningitis in suspected meningitis cases.

Material and methods: A total of 138 clinically suspected cases of meningitis admitted to NSCB medical college hospital Jabalpur were studied. All the cases were examined clinically and their CSF and blood samples were obtained for various investigations after taking consent in written Performa. CSF ADA levels were measured in all cases using Spectrophotometric method.

Result: Statistically significant higher values of CSF- ADA were observed with Tubercular Meningitis compared to Pyogenic Meningitis and Viral meningitis cases ($p<0.001$). The sensitivity and specificity was 96.4% and 96.4% respectively when a cut-off value of ADA of 11U/l was used. The PPV, NPV and accuracy of ADA test in diagnosing Tubercular Meningitis was 97.6, 94.6 and 96.4 respectively.

Conclusion: We concluded that CSF- ADA level can be used as simple, rapid, inexpensive test for early diagnosis of tubercular meningitis and differentiating it from pyogenic and viral meningitis.

Keywords: CSF-ADA, Differential Diagnosis of Meningitis

INTRODUCTION

Among the patients with meningitis, tubercular meningitis is an important cause of morbidity and mortality in India and other developing countries. Due to lack of early diagnosis, fatality is high in positive cases and sequel of disease may be distressing and disabling in the non-fatal cases. Global burden of tuberculosis is still high, particularly in developing countries; and globally, there were an estimated 9.27 million new cases(139/100,000 population) of tuberculosis in 2007, and the number of prevalent cases was 13.7million (206/100,000 population).[1] 9 Incidence rates of tubercular meningitis are age specific and range from 31.5/100,000 (<1 year) to 0.7 per 100,000 (10-14 year) in the Western Cape Province, South Africa.[2] The estimated mortility due to tubercular meningitis in India is 1.5/100,000 population.[3] Adenosine deaminase is an enzyme of purine metabolism pathway that catalyzes hydrolytic deamination of adenosine to inosine and ammonia. ADA has 2 isoenzymes ADA1 and ADA2. ADA2 is the major component (73%) of the activity of total ADA in the serum of healthy persons. ADA has much greater affinity for adenosine and foundonly in lymphocytes, macrophages and monocytes, which release it when stimulated in the presence of live organisms.[4]

Many literature has shown that CSF ADA levels can differentiate various types of meningitis. Various investigators have shown that the levels of ADA could be sensitive and specific in diagnosis of tubercular meningitis.[5-7] Aim of the present study is to evaluate whether ADA levels can be used to differentiate various types of meningitis in suspected meningitis cases.

MATERIAL AND METHODS

A total of 138 clinically suspected cases of meningitis admitted to NSCB medical college hospital Jabalpur were studied. All the cases were examined clinically and their CSF and blood samples were obtained for various investigations after taking consent in written Performa. The present study was approved by the scientific and ethics committee of NSCB Govt. medical college and hospital Jabalpur(MP)

Following investigations were done-

- Hematological- Hb, TLC.
- Biochemical- RBS.
- CSF- Physical examination, biochemical(Protein, sugar), Microscopic examination, bacteriological exam(AFB and Gram stain)
- Neuroimaging
- CSF ADA level using Spectrophotometric method

Inclusion criteria

Patient of all age group with suspected sign, symptoms and clinical features suggestive of meningitis.

Exclusion criteria

- Patient already on treatment of meningitis
- Patients with acute infection at sites other than CNS.
- Patient in whom lumbar puncture is contraindicated
- Associated sever hepatic dysfunction
- Females on oral contraceptives and intrauterine device
- Sever dyslipidemia and patients on steroid treatment.

Estimation of ADA in CSF: Turbidimetry method was used for ADA estimation.

STATISTICAL ANALYSIS

The data were analyzed using chi square test with the help of SPSS 20 software. The critical levels of significance of the results were considered at 0.05 levels i.e. $P<0.05$ was considered significant.

RESULT

In the present study 138 patients of clinically suspected

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meningitis were included of which there were 83 cases of Tubercular Meningitis, 24 cases of Viral meningitis and 31 cases of Pyogenic Meningitis.

In the present study the lowest age was <1 month and the highest was 75yrs. The mean age of study group was 24.16year. Table-1 describes the age wise distribution of cases with maximum No of cases (35) in age group 30-45yrs followed by second peak in age group <0-5 and 15-29yrs age group with 33 cases in each group. The mean age for TBM was 26.96±19.49, mean age for VM was 20.17±16.99 and mean age for PM was 19.76±21.55. Statistically no significant difference was seen (p>0.05).

Table-2 shows gender wise distribution in meningitis cases. There were 73.5% male and 26.5% females in TBM 62.5% male and 37.5% females in VM and 61.3% male and 38.7% females in PM group. Overall male case were more in number compared to female in our study however there were no statistically significant difference seen (p>0.05%).

Table-3 depict the ADA values in meningitis cases. Value of ADA were 12.28313±2.034748 in Tubercular Meningitis, 2.658065±0.349069 in Pyogenic Meningitis cases and in Viral Meningitis cases value were 1.991667+0.239414. Statistically significant higher values were observed with Tubercular Meningitis compared to Pyogenic Meningitis and Viral Meningitis cases (p<0.001). The sensitivity and specificity was 96.4% and 96.4% respectively when a cut-off value of ADA of 11U/l was used. The PPV, NPV and accuracy of ADA test in diagnosing TBM was 97.6, 94.6 and 96.4 respectively.

DISCUSSION

In developing countries like India where tuberculosis is very common early diagnosis of TBM and institution of correct therapy early in the course of disease can prevent serious neurological manifestations and can considerably reduce the morbidity and mortality. On routine CSF examination many a time it is difficult to differentiate between TBM and viral meningitis. The only confirmatory test for TBM is demonstration of tubercle bacilli in AFB smear and on culture. But AFB smear is not positive in all cases and culture takes 4-6 weeks, which can delay the treatment and serious complication can develop. So there is need for rapid confirmatory test for early diagnosis of TBM. Our study aimed at evaluating the diagnostic role of CSF ADA level in TBM. In the present study out of total 138 patients, 83 patients were diagnosed as tubercular meningitis based on the clinical features and CSF analysis. The mean ADA activity was 12.28 ± 2.03 U/l in the tubercular meningitis group, 2.65= 0.34 in pyogenic meningitis group and 1.99±0.23 in the viral meningitis group. Comparing the ADA activity, the difference was found to be statistically significant (p<0.001) in the tubercular meningitis compared to non tubercular meningitis. The sensitivity and specificity was 96.4% and 96.4% respectively when a cut- off value of ADA of 11 U/l was used. CSF- ADA levels were considerably higher in tubercular meningitis compared to viral meningitis and pyogenic meningitis. The results were concurrent with the other studies.[8-11] Choi SH et al studied ADA activity in CSF of 182 patients with meningitis. The mean ADA level in tubercular group was 12.7±7.5 U/l and it was significantly higher than the other groups (3.10±2.9 U/l; p<0.001). The sensitivity and specificity was 83.0% and 95.0% respectively when a cut-off value of 7 U/l was used.[5] Pettersson et al reports sensitivity of 100.0% and specificity of 99.0% when a cut-off value of 20 U/l was used, but in that study there were only 3 enrolled tubercular meningitis patients.[6] Chotmongkol V et al identified a CSF ADA level of 15.5U/l as the best cut-off value to differentiate tubercular meningitis and non-tubercular meningitis, with sensitivity of 75% and specificity of 93.0%.[7]

In our study, we found that the mean value of CSF ADA was 2.65± 0.34 in pyogenic meningitis. Some studies have reported a lower efficacy of this test and show an overlap between tubercular meningitis and bacterial meningitis.[12,13] So we used the higher cut-off value of 11U/l in order to increase the sensitivity of ADA. In our study the level of ADA in CSF is considerably high in tubercular meningitis compared to pyogenic and viral meningitis at a cut-off of 11U/l. So we concluded that CSF-ADA level can help in the differentiation of tubercular meningitis from non-tubercular meningitis. However, they should be interpreted judiciously in the light of the patients' clinical manifestations and the CSF physical, biochemical and microscopic characteristics.

Age(years)	TBM (n=83)	VM (n=24)	PM (n=31)
<0-5	14(16.9%)	6(25.0%)	13(41.9%)
6-14	9(10.8%)	5(20.8%)	2(6.5%)
15-29	22(26.5%)	4(16.7%)	7(22.6%)
30-45	25(30.1%)	7(29.2%)	3(9.7%)
46-59	5(6.0%)	1(4.2%)	4(12.9%)
>60	8(9.6%)	1(4.2%)	2(6.5%)
Mean±SD	26.96±19.49	20.17±16.99	19.76±21.55

Table-1: Age distribution in cases of meningitis

Sex	TBM (n=83)	VM (n=24)	PM (n=31)
Male	61(73.5%)	15(62.5%)	19(61.3%)
Female	22(26.5%)	9(37.5%)	12(38.7%)

Table-2: Gender wise distribution in cases of meningitis

	TBM (n=83)	PM (n=31)	VM (n=24)
ADA (U/L)	12.28313±2.034748	2.658065±0.349069	1.991667±0.239414

Table-3: Levels of ADA in Meningitis

CONCLUSION

We concluded that CSF-ADA activity was higher in patients with tubercular meningitis as compare to pyogenic and viral meningitis. So it can be used as simple rapid inexpensive test for differentiating tubercular from pyogenic and viral meningitis

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