ORIGINAL RESEARCH PAPER
Volume - 9 | Issue - 8 | August - 2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

STUDY OF ADENOSINE DEAMINASE ACTIVITY IN CEREBROSPINAL FLUID FOR DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF TUBERCULOUS MENINGITIS

Pathology

Dr Vibha Rasesh Vyas (MD. (Path & Bact))Assistant Professor, Oncopathology ,GCRI,Ahmedabad

Dr Biren Parikh* (DCP,MD(Pathology), MBA)Associate Professor, Oncopathology, GCRI, Ahmedabad
*Corrsponding Author

ABSTRACT

Introduction : To study cerebrospinal fluid (CSF) adenosine deaminase (ADA) activity in meningitis cases for diagnosis and differential diagnosis of Tuberculous meningitis. **Material and Method:** The study was conducted in 100 cases & divided in different patient groups by relevant investigations. CSF ADA estimation was done by spectrophotometry. **Result:** Statistically significant higher values of CSF ADA were observed with TBM compared to pyogenic meningitis and aseptic meningitis ($p<0.001$). The sensitivity and specificity was 96% and 100% respectively when a cut off value of ADA 9 IU/L was used. The PPV , NPV, and accuracy of ADA test in diagnosing TBM was 100%, 96.15% and 98% respectively. **Conclusion :** Our study concluded that CSF ADA level can be used as simple , rapid and inexpensive test for diagnosis of TBM.

KEYWORDS

INTRODUCTION

Tuberculous meningitis (TBM) is a major health problem all over the world and its incidence is 7-12% of all patients suffering from tuberculosis in all developing countries (1,2). Early diagnosis and treatment are very important because it can lead to irreversible central nervous system (CNS) damage if remain untreated (1). For diagnosis of TBM, we need clinical history with detection of acid fast bacilli (AFB) by methods based on phenotypic and genotypic techniques (3). Light microscopy is a commonly used rapid method for detection of AFB in a smear with high specificity but its sensitivity is only 30-40% (3). Culture on Lowenstein Jansen (L-J) medium is more sensitive than light microscopy but the incubation period is very long (3). Many newer techniques in form of genotypic assays are available i.e. Genprobe amplified Mycobacterium tuberculosis direct test, Roche Amplicor MTB test, Cobas Amplicor test and Abbott LCX test. But all are very expensive (3). In this situation, there is a need to develop a more rapid, sensitive and cost-effective method for diagnosis of TBM (2). Adenosine Deaminase (ADA) is an enzyme related to purine metabolism and these enzyme levels are found to be higher in T lymphocytes than that in erythrocytes (2). T cells release ADA in response to tubercule bacilli while cell-mediated Immunity (3). According to literature, cerebrospinal fluid adenosine deaminase (CSF ADA) is very helpful in the differential diagnosis of various types of meningitis with sensitivities and specificities ranging from 44-100% and 71-100% respectively (2,5). Cerebrospinal fluid adenosine deaminase levels are also useful to predict outcome in patients suffering from TBM as CSF ADA levels have a good correlation with the stage of the disease (2).

AIMS AND OBJECTIVES:

1. To check the efficacy of CSF ADA estimation as a diagnostic tool for the diagnosis and differential diagnosis of TBM.
2. To evaluate the use of CSF ADA activity for early diagnosis of TBM.
3. To determine sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CSF ADA as a diagnostic test for TBM.

MATERIAL & METHOD

In the present prospective study CSF ADA estimation was carried out in 100 cases. Age range was 0 to 12 years. Clinically there were neurological involvement suggestive of meningeal infection or involvement in test group. We had 30 cases of control group who has no meningeal infection. The study was conducted at the Government Medical college. In all patients, we performed hematological investigations like complete blood count (CBC), erythrocyte sedimentation rate (ESR), blood culture, radiological investigations like x-ray chest, computerized tomography (CT) scan of brain. We also included fundus examination and, mountoux test (BCG test). We also performed cerebrospinal fluid (CSF) examination, which includes physical analysis, biochemical analysis, microscopic analysis and ADA level estimation. All the findings were categorized in following five groups.

1) Group 1: Tuberculous Meningitis (50 cases): Cerebrospinal fluid showing pleocytosis with predominantly lymphocytes, CSF Protein > 40mg/dl, CSF sugar < 40 mg/dl or < 2/3 of random blood sugar. Radiological evidence of tuberculosis and/or positive montoux test.

Patient who has history of contact with tuberculous patients/history suggestive of tuberculosis or evidence of tuberculosis in other site of the body with signs of meningeal irritation.

2) Group 2: Pyogenic Meningitis (30 cases): Acute onset with clinical picture and CBC suggestive of pyogenic infection. Cerebrospinal fluid showing pleocytosis with predominantly Polymorphs, CSF protein was increased, CSF sugar was decreased/absent.

Group 3: Aseptic Meningitis (10 cases).

Group 4: Other CNS disorders (10 cases).

Group 5: Control cases (30 cases): Patients without any neurological disorder who had to be given spinal anesthesia were included as control.

For each Patient CSF was collected in single plain bulb and one fluoride bulb for physical, biochemical and cytological examination. Cerebrospinal fluid ADA level was measured by spectrophotometric method based on the principle of Guisti & Galanti method of enzymetic analysis (11). Exclusion criteria includes hemorrhagic CSF as liberation of ADA from red blood cells lead to false positive values.

Observation

In the present study Male (72 cases) & Female (28 cases) with M:F 2.5:1 showing male preponderance.

Table 1: Distribution of cases with regards to AGE group & clinical diagnosis.

Age	Control	TBM	PyoM	Aseptic M	Other CNS dis.
Months	No of cases	No of Cases (%)	No of Cases (%)	No of cases (%)	No of Cases (%)
0-6	01	03 (06)	02 (6.6)	1 (1 0)	0 (0)
7-12	02	12 (24)	07 (23.3)	1 (10)	1 (10)
13-24	03	11 (22)	05 (16.6)	4 (40)	2 (20)
25-60	05	15 (30)	08 (26.6)	2 (20)	2 20)
61-84	09	03 (06)	05 (16.6)	1 (10)	2 (20)
84-144	10	06 (12)	03 (10)	1 (10)	3 (30)
Total	30	50 (100)	30 (100)	10 (100)	10 (100)

It is evident from above table 1 that in TBM, among pediatric age group, maximum number of cases were observed in age 13-60 months.

Three patients were observed in age group below 6 months.

Table 2: Results of CSF ADA estimation

Study Group	No of cases	CSF ADA IU/L Range	CSF ADA IU/L Mean ± SD
Control	30	0.3-1.1	0.65 ± 0.25
TBM	50	7.0-16.3	11.55 ± 2.80
Pyo M	30	1.4-6.0	2.17 ± 0.86
Aseptic M	10	0.8-1.5	1.1 ± 0.04
Other CNS disorder	10	0.3-0.8	0.52 ± 0.02

As shown in Table CSF ADA levels expressed as Mean ± SD of mean. The mean CSF ADA levels were found to be increased in all three types of meningitis (Tubercolous, Pyogenic, Aseptic) compared to other CNS disorders and control subjects. However, rise in TBM was more significant. The difference in mean CSF ADA levels between TBM and other groups (Pyogenic meningitis, Aseptic meningitis, other CNS disorders was also remarkable.

The statistical data suggest that the difference of mean of CSF ADA level between TBM group and control subject is highly significant (P<0.001). The difference of mean CSF ADA level between TBM group and pyogenic meningitis group is also statistically highly significant(P<0.001). The difference in mean CSF ADA level between TBM group and aseptic meningitis group is also highly significant (P <0.001). The difference in mean CSF ADA level between TBM group and other CNS disorders group is also statistically highly significant (P<0.001).

In present study maximum number of patients of TBM were having CSF ADA levels in the range of 10-11 IU/L and 12-13 IU /L while none of the patient of non-tuberculous CNS disease (pyogenic meningitis, aseptic meningitis , other CNS disorders) group was showing the CSF ADA levels above 9 IU / L , so on considering 9 IU / L of CSF ADA as cut off level , 48 patients of TBM were showing CSF ADA levels above 9 IU/L so considered as True Positive cases and 2 patients were showing CSF ADA levels below 9 IU/L so considered as False Negative cases.

DISCUSSION

Tuberculosis is very common in India and the most serious form of extrapulmonary TB is Tuberculous Meningitis (2,12). Amongst the cases of TBM the clinical presentation is variable, so an early diagnosis with immediate treatment is necessary to prevent serious sequele (2).

ADA is an enzyme, of purine catabolism which plays an important role in the catabolism of Monocytes, Macrophages and T Lymphocytes. ADA levels were found to be increased in Tuberculosis and other infections in which the cell mediated immunity is actually involved (2). ADA levels estimation in plueral fluid, peritoneal fluid and in CSF has been accepted as an important marker for diagnosis of extrapulmonary tuberculosis in different studies(2). CSF ADA levels were found to be useful for diagnosis of TBM and for differentiating TBM from normal subjects or other meningitis and other neurological disorders(3).

The present study was conducted to confirm the usefulness of CSF ADA estimation for diagnosis of TBM. In the present study, the range of CSF ADA level in TBM cases was 7.0-16.3 IU/L with a mean of 11.55 ± 2.80 and in non TBM cases it was quite low i.e. in pyogenic meningitis range of CSF ADA level was 1.4-6.0 IU/L with a mean of 2.17 ± 0.86 ; in aseptic meningitis range of CSF ADA level was 0.8-1.5 IU/L with a mean of 1.1 ± 0.04 and in other CNS disorders the range of CSF ADA level was 0.3-0.8 IU/L with a mean of 0.52 ± 0.02. The difference in CSF ADA value was highly significant (p value <0.0001) between the study groups similar to the study by Chander et el (10).

Results of the present study indicate that ADA levels in CSF with a cut off value of 9.0 IU/L had a high accuracy to differentiate TBM from non TBM cases with a sensitivity of 96% , specificity of 100% ,Positive Predictive Value(PPV) 100 % , Negative Predictive Value (NPV) 96.15 % and Accuracy 98 %.

Table 3: Comparative Analysis of our study with different authors is tabulated as below:

	No case	Mean ± SD	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Present study	50	11.55±2.80	96	100	100	96.15	98
Puri et el (2)	40	17.89±9.59	92.5	89.32	77.08	96.84	
Mishra et el(4)	27	9.4 ±5.4	88.9	92.3	88.9	92.3	90.9
Sharad et el(5)	83	12.28±2.03	96.4	96.4	97.6	94.6	96.4
Rajesh et el(9)	24	12.23±4.92	95.83	92.85	95.83	92.85	94.73
Chander et el(10)	28	16.46±6.24	82.14	90.91	92	80	86

In comparison with different authors our study has good sensitivity (96%) and specificity (100%) with positive predictive value 100%, negative predictive value 96.15% and accuracy 98%.

CONCLUSION

The present study concluded that Mean CSF ADA level in TBM was significantly higher (p<0.001) than other meningitis and control group. CSF ADA estimation is simple, rapid, least invasive & less expensive laboratory investigation for diagnosis of TBM and therefore CSF ADA estimation may find a place as routine investigation for diagnosis of TBM.

REFERENCES

1. Khanna A., Atam V., Patel M.,Verma R., and Gupta A.:Evaluation of Cerebrospinal Fluid adenosine deaminase levels as an ancilliary diagnostic test for tuberculous meningitis and its correlation with adverse neurological outcome. Annals of Nigerian Medicine,Jul-Dec 2010,Vol 4, Issue 2;51-54.
2. Saini P., Dosi P., Gambhir S., Gupta P. and Tignath G.: Raised Adenosine Deaminase in the Cerebrospinal Fluid. A tool for the Diagnosis of Tuberculous Meningitis in Developing countries. Nigerian Postgraduate Journal, Vol 24, Issue 1, January-March 2017;56-59.
3. Gupta BK.,Archit B., Bandyopadyay D., Baruah H.: Adenosine Deaminase Levels in CSF of Tuberculous Meningitis patients. J Clin Med Res. 2010;2(5):220-224.
4. Mishra O.P., Chandra L. et el: Cerebrospinal fluid Adenosine Deaminase Activity for the Diagnosis of Tuberculous Meningitis in children. Journal of Tropical Pediatrics Vol 42, June 1999; 129-133.
5. Jain S., Sharma A., Nayak R.: Diagnostic Role of CSF-ADA in Differential Diagnosis of Meningitis. International Journal of Contemporary Medical Research Vol 3, Issue 8, August 2016, 2201-2203.
6. Prasad P., Chauhan S., Khurana B.: Evaluation of CSF ADA in diagnosis of Tuberculous Meningitis. International Journal of Contemporary Medical Research Vol 5, Issue 1,January 2018;06-10.
7. Jerome H. Chin: Tuberculous Meningitis Diagnostic and therapeutic challenges. Neurol Clin Pract. 2014 Jun ;4(3) :199-205.
8. M.E.Torok: Tuberculous Meningitis : Advances in Diagnosis and Treatment. Br Med Bull 2015 March ;113; 117-131.
9. Baheti R., Laddha P. and Gehlot RS : CSF Adenosine Deaminase(ADA) Activity in various types of meningitis. Journal, Indian Academy of Clinical Medicine. Vol 2, No. 4, Oct-Dec 2001; 285-287.
10. Chander A., Shrestha CD.: Cerebrospinal fluid adenosine deaminase levels as a diagnostic marker in tuberculous meningitis in adult Nepalese patients. Asian Pac J Trop Dis 2013; 3(1):16-19.
11. Guisti G.: Adenosine deaminase in methods of enzymetic analysis. Editor Bergmeyer HU. 2nd Edition, New York, Academic Press, 2:1092-1099, 1974.
12. Prasad R., Khanna BK, Mukerji PK, Agarwal SK and Shrivastva VML : Adenosine Deaminase activity in cerebrospinal fluid for diagnosis of Tuberculous Meningitis. Ind J Tub.,38;99-102,1991.