

Original Research Article

Comparative analysis of cerebrospinal fluid adenosine deaminase levels in infective meningitis of different aetiologies

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ABSTRACT

Background: Meningitis can be caused by bacteria, viruses, parasites, and fungi as well as by non-infectious conditions including inflammatory disorders (e.g., systemic lupus erythematosus or Kawasaki disease) and neoplasia (e.g., leukemic meningitis). The objective of this study were to study cerebrospinal fluid (CSF) adenosine deaminase (ADA) levels in infective meningitis of different aetiologies. And to assess the role of cerebrospinal fluids (CSF) adenosine deaminase (ADA) levels in differentiating tubercular from non-tubercular meningitis.

Methods: The study was conducted on 70 patients of meningitis at Postgraduate Department of Paediatrics, in G. B. Pant Hospital, an associated hospital of Government Medical College Srinagar. Out of 70 patients included in the study 27 cases were Aseptic Meningitis (AM), 14 cases partially treated pyogenic -meningitis (PTM), 19 cases pyogenic meningitis (PM), and 10 cases were tubercular meningitis (TBM). ADA activity of CSF was quantified by colorimetry.

Results: In our study we observed a significant high level of ADA 30.0 ± 3.2 U/L (20.0, 54.0) among the tubercular meningitis (TBM) patients and its respective level among Aseptic Meningitis (AM), was 8.1 ± 0.3 U/L (4.0, 11.5), partially treated pyo -meningitis (PTM) was 7.6 ± 0.4 U/L (5.0, 11.0), pyogenic meningitis (PM) was 11.6 ± 0.5 U/L (8.0, 14.5). In total Non-TBM ADA level was 9.1 ± 0.3 U/L (4.0, 14.5) units/liter. At cut off of $>$ or equal to 10U/L sensitivity was 100% specificity 66.67% positive predictive value 33.33% negative predictive value of 100% diagnostic accuracy 71.43%. At a higher cut off of $>$ or equal to 12U/L sensitivity was 100% and specificity increased to 81.67% positive predictive value 47.62% negative predictive value 100% diagnostic accuracy was 84.29%.

Conclusions: The sensitivity and specificity of CSF ADA activity is markedly high in differentiating TBM from non-TBM. Hence CSF ADA activity may be used as a simple, cost-effective and reliable test for early diagnosis of TBM.

Keywords: Adenosine deaminase, Cerebrospinal fluid, Tubercular meningitis

INTRODUCTION

Meningitis can be caused by bacteria, viruses, parasites, and fungi as well as by non-infectious conditions including inflammatory disorders (e.g., systemic lupus erythematosus or Kawasaki disease) and neoplasia (e.g., leukemic meningitis).^{1,2} Tuberculosis kills 2.7 lakhs annually every year in India as per the Global Report on

Tuberculosis 2013, there were an estimated 5,30,000 TB cases among children (under 15 years of age) and 74000 TB deaths (among HIV-negative children) in 2012 (6% and 8% of the global totals, respectively).^{2,3} Delay in the diagnosis and so in initiation of specific treatment, results in poor prognosis and 25% of such patients are cured with residual permanent sequelae.^{3,4} Tuberculous meningitis (TBM) is affecting the children more and

more and has acquired an endemic shape; more so in poor socio-economic group. Incidence of TBM is 7-12% in developing countries. Tuberculous meningitis complicates about 0.3% of untreated tuberculosis infections in children.⁶ It is most common in children between 6 months and 4 year of age.⁶ The prognosis of tuberculous meningitis correlates most closely with the clinical stage of illness at the time treatment is initiated, clearly influenced by the development of an accurate, reliable and rapid diagnostic test. Available methods of diagnosis of TBM were evaluated and most of them were shown to have low sensitivity and specificity.⁷

Acid-fast staining of CSF sediment is the most rapid method for detection of mycobacterium, but this method lacks sensitivity. The use of polymerase chain reaction (PCR) to detect mycobacterium tuberculosis specific DNA may be of potential value. However, the facility to perform the test is not available in all laboratories and is less sensitive. It has been suggested that adenosine deaminase (ADA) activity in CSF may help differentiate TBM from non-Tubercular meningitis.^{8,16,18-21} The measurement of ADA was initiated by Giusti in 1981 and applied extensively in clinical practice.⁹ Present in virtually all mammalian cells, its primary function in humans is the development and maintenance of the immune system.¹⁰ The chief physiological function of ADA is related to lymphocytic proliferation and differentiation.¹¹⁻¹³ Numerous previous studies have demonstrated that CSF-ADA estimation is useful in the diagnosis of TBM and can differentiate TBM from normal subjects or from patients with other neurological disorders.¹⁴⁻¹⁸ However, the significance of ADA level in CSF was variable from a few studies, which was the conceiving idea for taking up this study.¹⁵

The objective of this study were to study cerebrospinal fluid (CSF) adenosine deaminase (ADA) levels in infective meningitis of different aetiologies. And to assess the role of cerebrospinal fluids (CSF) adenosine deaminase (ADA) levels in differentiating tubercular from non-tubercular meningitis.

METHODS

Design of this study was a Hospital based cross-sectional, analytical design conducted at Post-Graduate Department of Paediatrics, in G. B. Pant Hospital, an associated hospital of Government Medical College Srinagar for a period of 12 months from 1st April 2013 to 31st March 2014. The hospital is a tertiary care referral centre having catchment area of both rural and urban populations. The nature and the purpose of procedure was explained to the parents/guardians. A written informed consent from parents was taken in all cases.

Inclusion criteria

The patients fulfilling the inclusion criteria between the ages of 2 months to 12 years suspected of central nervous

system infection were admitted in the study. Enzyme activity was measured in CSF of four groups of patients with each group having their own inclusion criteria.

Pyogenic meningitis (PM) group

In this group, CSF of patients showing organisms in gram stained smear or culture was taken as diagnostic criteria. In the absence of organisms CSF showing pleocytosis of more than 100 cells/mm³ predominantly polymorphs, sugar less than half of blood sugar and protein more than 60 mg % was taken as inclusion criteria.

Partially treated pyogenic meningitis (PTM) group

This group consisted of patients in whom CSF showed presence of organisms on gram stained smear or culture. In the absence of organism CSF showed pleocytosis of more than 100 cells/mm³, sugarless than half of blood sugar, protein more than 60 mg % and who had received I.V. antibiotics for pyogenic meningitis for more than 48 hours before coming to hospital.

Aseptic meningitis (AM) group

This group consisted of patients whose CSF showed absence of organisms on gram stain and culture and CSF showed pleocytosis of more than 10 cells/mm³ with predominance of lymphocytes and sugar more than 2/3 of blood sugar value.

Tuberculous meningitis (TBM) group

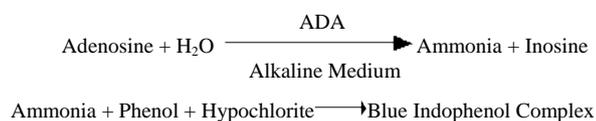
In this group the patients had two or more of the following features including signs and symptoms of meningitis; fever for > two weeks, contact with an adult with tuberculosis, positive Montoux test. This group had CSF with absolute lymphocyte counts > 50 cells/mm³, protein more than 60 mg % and sugar less than 2/3 of blood sugar, chest X-ray showing skiagram suggestive of pulmonary TB, isolation of AFB from any site, CT scan showing evidence of chronic meningitis like hydrocephalus, basal exudates, infarcts, tuberculomas and histological evidence of tuberculosis.

The selected patients underwent a detailed history and thorough clinical examination, followed by routine laboratory investigations including CBC, CRP/ESR, Chest X-Ray, Montoux test, Serum Electrolytes (Sodium, Potassium, Chloride, and Bicarbonate), Serum Calcium, and Serum Phosphorus, Blood Sugar, Blood Culture, KFT, LFT, Abdominal and Cranial USG, CT/CECT Brain MRI Brain where Ever Indicated. After a proper informed consent, CSF sample was taken by spinal tap, after excluding any contraindication like focal neuro-deficit, tapping site infection, brain tumour, hemicrainal headache, cranial nerve palsies, bleeding disorders, cardiovascular instability, raised intracranial pressure (except raised fontanel), and papilledema. 2 ml of CSF sample was collected in a sterile bottle at the time of

admission. CSF was divided into 3 parts one part for chemical analysis; one for cells, gram staining, acid fast bacilli staining (AFB), culture with sensitivity; and one part for enzyme activity. Enzyme activity was measured in CSF of four groups of patients i.e., Tubercular meningitis (TBM), partially treated pyo meningitis (PTM), Aseptic meningitis (AM) and pyogenic meningitis (PM). Activity of ADA was assayed according to the method of Guisti.⁹ The samples obtained were centrifuged at 2000 g for 10 min and the supernatant stored at -20°C until estimation. One unit of activity represented the deamination of one micromole of adenosine /min at 37°C and was expressed as U/L.

Principle of ADA test

ADA activity in CSF was determined at 37°C according to the method of Giusti and Galanti, based on the Berthlot reaction, that is the formation of colored indophenol complex from ammonia liberated from adenosine and quantified using colorimeter. One unit of ADA is defined as the amount of enzyme required to release 1 mmol of ammonia/min from adenosine at standard assay conditions.⁹ Results were expressed as units per litre per minute (U/L/min). Adenosine deaminase hydrolyses adenosine to ammonia and inosine. The ammonia formed further reacts with a phenol as hypochlorite in an alkaline medium to form a blue color indophenol complex with sodium nitroprusside acting as a catalyst. Intensity of the blue colored indophenol complex formed is directly proportional to the amount of ADA present in the sample read by colorimeter at 570 to 630 nm.



Reference values

CSF	Normal	< 10U/L
	Positive	> 10 U/L

It is recommended that each laboratory establish its own normal range representing its patient population.

Exclusion criteria

- Patients in whom the lumbar puncture was traumatic were excluded from the study
- Concomitant illness such as HIV/on immunosuppressive therapy
- Conditions which can contribute in elevation of CSF ADA Activity in body fluids like – typhoid fever, infectious Mononucleosis, viral hepatitis, rheumatologic diseases intracranial tumours and lymph proliferative disorders were also excluded from the study.³⁹

Statistical analysis

Data was entered on Microsoft Excel. Continuous variables were summarized as mean and standard deviation. Categorical variables were summarized as percentages. One-way analysis of variance (One-Way ANOVA) was used to analyze mean differences among different diagnosis groups. Hochberg-GT2 was used as a multiple comparison test when group variances were similar. When group variances could not be assumed to be similar, Games-Howell was used for multiple comparisons. Analysis of covariance (ANCOVA) was used to control for the effect of blood sugar while analyzing the relationship between CSF sugar and Diagnosis. Bonferroni was used for post-hoc comparisons. To evaluate the value of ADA as a tool for diagnosis of tubercular meningitis, parameters were reported along with their 95% Confidence Intervals. The parameters reported included sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy and Cohen's Kappa. This part of the analysis was done using Open Epi ([http://www.openepi.com/DiagnosticTest.htm](http://www.openepi.com/DiagnosticTest/DiagnosticTest.htm)) SPSS 20.0 was used for analysis. A p-value of <0.05 was taken as significant.

RESULTS

A total of seventy patients admitted during this period fulfilled the inclusion criteria. Out of 70 patients included in the study 27 cases were aseptic meningitis (AM), 14 cases partially treated pyogenic -meningitis (PTM), 19 cases pyogenic meningitis (PM), and 10 cases were Tubercular Meningitis (TBM). The selected patients underwent a detailed history and thorough clinical examination, followed by routine laboratory investigations. Data was expressed as mean±SE, median and percentages. Patients were in between 6 and 144-month age, when the mean was 56.1±4.7 months and respective median was 48 months.

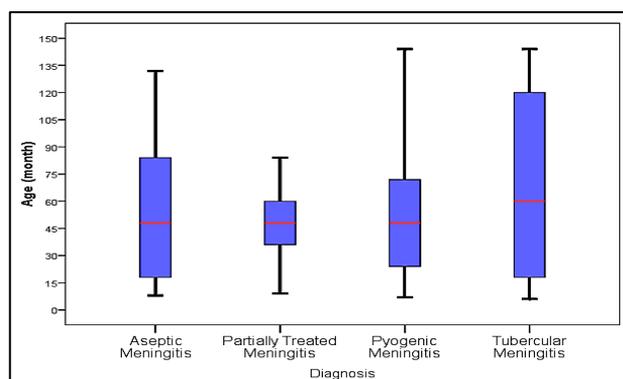


Figure 1: Meningitis type across age month.

Preponderance of 47 (67.1) males who were in between 8 and 144 month with the mean age of 59.6±5.7 months, did not differ (p>0.05) from 23 (32.9) females who were

in between 6 and 144 month with mean age 48.7±8.1 months.

Total CSF -cytology of TBM subjects was 748.0±214.0 (170, 2500) was considerably higher than that of AM 140±13.114 (27, 280) and PTM 163.43±15 (106, 250). Total CSF-cytology of PM1022.0±165.3 (300, 2700) in comparison to TBM was not significant. Moreover; T-cytology for all Non-TBM subjects 405.8±75.5 (18, 2700) in comparison to TBM was not significant. Polymorphs in CSF cytology of TBM subjects 31.0%±4.1 (10, 45) was considerably lower than that of AM 34.44%±2.3 (10, 50), PTM 65.71%±3.549 (50, 90), PM 71.32%±2.47.TBM in comparison to AM was not significant. Otherwise the difference was significant. Lymphocytes in CSF of TBM subjects 69.0%±4.1 (55, 90) was higher than that of AM 65.19% 2.20 (50, 90), PTM %34.29±3.549 (10, 50), PM %28.68±2.4 (5, 45). TBM in comparison to AM was not significant. Protein level of TBM subjects 136.4±36.8 (62, 460) was significantly higher than that of AM 42.48±1.193(30, 55) and PTM 63.43±1.6(55, 75) PM 101.05±5.992 (65, 155) or all the Non-TBM 70.0±3.6 (30, 155) subjects. With respect to CSF sugar when adjusted for blood sugar mean difference was significant when comparing AM with PM, PTM, TBM. We observed a significant high level of ADA 30.0±3.2 (20.0, 54.0) among the TBM cases. Its respective levels among AM was 8.1±0.3 (4.0, 11.5), PTM was 7.6±0.4 (5.0, 11.0), PM was 11.6±0.5 (8.0, 14.5) and all the non-TBM was 9.1±0.3 (4.0, 14.5) U/L. Each of the differences was significant (p<0.05).

Table 1: Results of post-hoc test for multiple comparisons (Games-Howell).

	Partially treated meningitis	Pyogenic meningitis	Tubercular meningitis
Aseptic meningitis	0.999	0.033	<0.001
Partially treated meningitis		0.042	<0.001
Pyogenic meningitis			<0.001

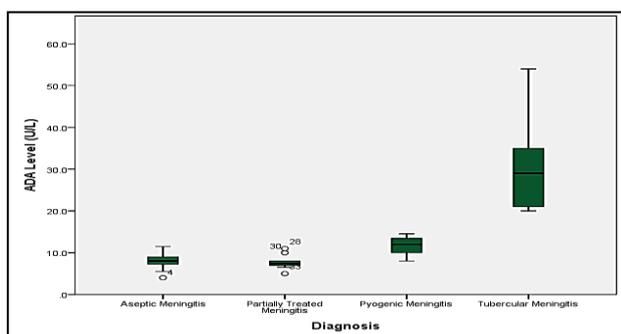


Figure 2: Box plot showing ADA levels across meningitis types in CSF.

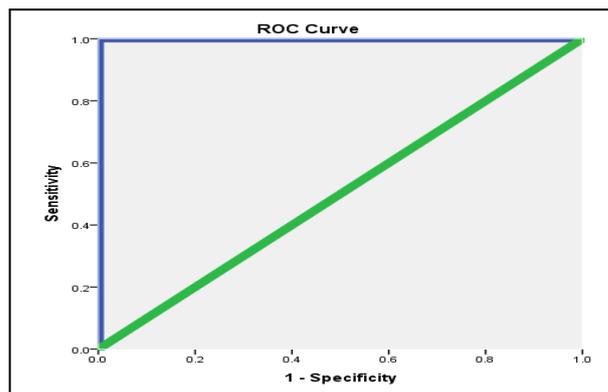


Figure 3: ROC Curve.

Correlation of ADA with CSF determinants was all through insignificant. 8 out of 10 cases of TBM had positive family history of tuberculosis X-ray chest was done in all the patients of suspected TBM of which 5 had skiagram suggestive of pulmonary tuberculosis. Contrast enhanced computerized tomography (CECT)was done in 68 (97.1) patients of which 21 (30.9) cases of non-TBM had features consistent with meningitis, and out of ten patients of TBM 4 had basal exudates, 3 had hydrocephalus, 2 had basal effacement and one meningeal enhancement. Out of ten cases of meningitis Montoux test was positive for 6 cases of Tuberculous Meningitis. USG (cranium) was done in 14 (20.0) subjects of which 1 (7.1) had hydrocephalus. BCG scar was present in 5 cases of TBM and was absent in other 5. Mtb PCR was positive in six out eight (6/8) cases of Tubercular Meningitis; in other two patients it was not done.

DISCUSSION

Demonstration or isolation of acid-fast bacilli on CSF smear or culturing of Mycobacterium which takes 4-6 weeks to show the growth is usually difficult.²⁴ Organisms may be recovered in culture of large volumes of CSF and in bacterial meningitis when patient comes after a course of antibiotics, organisms are usually not isolated.^{5,7} CSF cytology, biochemistry are other means to confirm the etiology but again, the results may overlap. Furthermore, newer methods to diagnose TBM such as bacterial genomic amplifications by Polymerase Chain Reaction or other comparable methods are not available for widespread use in the developing countries.

A total of seventy patients admitted during this period fulfilled the inclusion criteria. Out of 70 patients included in the study 27 cases were Aseptic Meningitis (AM), 14 cases partially treated pyo-meningitis (PTM), 19 cases pyogenic meningitis (PM) and 10 cases were tubercular meningitis (TBM).The common clinical presentations of meningitis observed in our study was Fever (98.6) followed by vomiting (81.4), headache (64.3), neck stiffness (60.0), kernings (31.4), altered sensorium (21.4), seizures (18.6), bulging anterior fontanel (12.9),

irritability (7.1) and Brudzinkis sign (4.3). Similar clinical presentations were also noted by Baheti R et al and Malla K et al but with different frequencies.^{22,31}

Mycobacterium couldn't be isolated in any of the TBM cases which differed from two studies of Gupta B K et al 6/29 and Pan A et al 1/32, however was consistent with Malla K et al 0/10.^{27,29,31} In our study in 2 out of 19 cases of pyogenic meningitis organisms were isolated from CSF culture, which included H influenzae and Streptococcus pneumoniae. Whereas in a study carried by Rana SV et al organisms were isolated from CSF culture in 2 patients out of 10 cases of pyogenic meningitis (PM) and Pan A et al 2/13.^{23,29} Bacterial isolates in CSF in our study was less than that observed in other studies but were quite similar in relation with some other studies.^{23,27,29,31}

The CSF total count (1022.0±165.3) and neutrophil count (71.32±2.47) in pyogenic meningitis was highest. CSF Sugar was lowest (35.344) while the CSF lymphocyte (69.0±4.1) and Protein (136.4±36.8) were highest in TBM. Rana SV et al and Pan A et al study groups pyogenic meningitis had the highest mean cell counts and TBM group had the highest mean protein values.^{22,29} Malla K et al analysed the CSF total count (903.28±1419.73) and neutrophil count (84.18±12.26) in PM was highest.³⁶ CSF sugar was lowest (29.15±15.11) in PM while the CSF lymphocyte (90.60±8.11) and Protein (256.90±203.61) were highest in TBM, These results are comparable to our study. These significant parameters may be additional supporting investigations to further differentiate different types of meningitis.

The mean level of ADA in our study was 30.0±3.2 (20.0, 54.0) among tubercular meningitis (TBM) cases. Its respective levels among aseptic meningitis (AM) was 8.1±0.3 (4.0, 11.5), partially treated pyogenic meningitis (PTM) was 7.6±0.4 (5.0, 11.0), pyogenic meningitis (PM) was 11.6±0.5 (8.0, 14.5) and all the Non-TBM cases was 9.1±0.3 (4.0, 14.5) U/L. Each of the differences was statistically significant (p<0.05).

Rana SV et al in their analysis found mean±SE ADA levels in Tubercular meningitis (TBM) of 18.22±3.35 (1.0-96.7), partially treated pyogenic meningitis (PTM) 6.28±0.91 (3.0-11.1), pyogenic meningitis (PM) 7.98±3.56 (0.3-29.0), Aseptic meningitis (AM) 3.43±0.86 (0.1-08.5), This difference of ADA values in CSF between TBM and other types of meningitis was statistically significant (p<0.01) which is comparable with our study.²³

Gupta BK et al in their analysis found that tuberculous group ADA activity in CSF ranged between 9.2 to 110 U/L with a median of 22, mean±SD as 27.1684±22.4563 while in non-tuberculous group ADA activity ranged between 2 to 10.5 U/L with a median of 6, mean±SD as 6.0619±2.5399, which is comparable with our study.³⁴

Malla K, et al in their analysis found that mean±SD with range of CSF-ADA was respectively 48±20.37 IU/L (20-70 IU/L), 14.57±6.48 IU/L (2-28 IU/L), 6.40±2.17 IU/L (3-9 IU/L), 8.29±10 IU/L (3-11 IU/L) and 5.27±2.69 IU/L (2-7 IU/L) in tubercular meningitis (TBM), pyogenic meningitis (PM), partially treated pyogenic meningitis (PTM), viral meningitis (VM) and controls and the value was highest in TBM which is comparable with our study.³¹

Pan A et al Mean ADA levels in CSF of TBM patients were higher (15.42 U/L) as compared to 7.21 U/L, 6.41 U/L and 7.50 U/L in PTM, AM and PM respectively which is comparable with our study.²⁹

This lower mean ADA activity in other studies may be due to the racial difference or difference in the method of estimation of ADA values.

The sensitivity and specificity of CSF ADA at a cut off 10 IU/L in our study was 100% and 66.67%, negative predictive value 100%, diagnostic accuracy of 71.43%. Other studies have shown sensitivity ranges of 44-100% and specificities of 75-99% for total ADA (by using 8 to 20 IU/L as cut off value for diagnosis.^{21,36,38} The sensitivity, negative predictive and diagnostic accuracy value of CSF-ADA for TBM increased if the cut off value was increased without changing the specificity in our study group. In TBM group, levels of ADA in CSF was correlated with cell counts, clinical and biochemical parameters but we found no correlation. There was no significant variation in ADA levels of CSF of TBM patients with immunization (BCG +ve and BCG -ive) and Montoux status.

CONCLUSION

This study demonstrates that ADA concentration in the CSF of meningitis patients, can be useful in differentiating tubercular meningitis from other types of meningitis i.e., pyogenic meningitis (PM), partially treated pyogenic meningitis (PTM), aseptic meningitis (AM). Furthermore, considering the diagnostic limitations of conventional CSF variables (proteins, glucose and cells) especially when stain and culture are negative, the CSF-ADA can provide pertinent, rapid and reliable diagnostic information, in TBM, which is particularly appropriate for areas lacking adequate laboratory facilities. Hence ADA estimation in CSF is simple, inexpensive, rapid, fairly specific method for making a diagnosis of tubercular meningitis. ADA estimation in CSF of TBM patients should find a place in routine laboratory methodology.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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