

Study of C-Reactive Protein & Adenosine Deaminase Levels in CSF Analysis of Patients with Meningitis

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Abstract

Background and Objectives: CNS infections continue to pose challenges to the treating physician. It is essential to make an accurate etiological diagnosis and institute appropriate treatment at the earliest in such cases. This requires diagnostic tests which can help differentiate the various forms of meningitis. CSF C-Reactive Protein and Adenosine Deaminase are two such tested parameters to differentiate the types of meningitis, and it is observed that ADA is elevated in tuberculous meningitis and CRP in pyogenic meningitis. Our objective was to assess the combined utility of these tests in our setup and to ascertain an optimal cut-off value for Adenosine Deaminase.

Method: 50 patients who were diagnosed with meningitis based on clinical features and routine CSF analysis, during the study period were selected. ADA and CRP levels in CSF of these patients were analysed.

Results: In our study out of 50 patients, 22 were diagnosed with tuberculous, 20 with viral and 6 with pyogenic meningitis. The mean ADA levels were 17 ± 8.5 IU/L in the tuberculous meningitis group which was higher than the other groups and this was statistically significant (p value-0.003).

With a cut-off value of 10IU/L, sensitivity & specificity of ADA in our setup was 86% and 63.63% respectively. Using an ROC curve analysis a more optimal cut-off value of 12.9IU/L was suggested.

The mean CRP values was 3.22 ± 1.9 mg/L in pyogenic meningitis and the value was significantly higher (p-value < 0.0001) than the other groups. The sensitivity and specificity of CRP in our setup was 83% and 71% respectively.

Conclusion: ADA levels are elevated in CSF of patients with tuberculous meningitis and CRP levels in patients with pyogenic meningitis. In view of low specificity of ADA, caution may have to be exercised in utilizing the test. Calculation of optimal cut-off at different setups may improve decision making

Keywords: CSF; C-Reactive Protein; Adenosine Deaminase; Pyogenic Meningitis; Tuberculous Meningitis

Background

In the modern medical world there is a constant fight against infectious diseases of various forms. Infectious diseases affect almost every organ system of the human body infections involving the central nervous system

being one of the many. CNS infections continue to pose significant challenges to the medical field.

Meningitis is the most common form of neuro infection. Aetiology of meningitis varies—viral, bacterial tuberculous etc.1 Differentiation of different forms of meningitis becomes essential to provide appropriate treatment.

Therefore, reliable and cost effective methods are essential to differentiate the various forms of meningitis and more so for rapid diagnosis.

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CRP and ADA levels in CSF are two such widely studied parameters to aid in early diagnosis of meningitis.

Studies conducted worldwide suggests that CRP level in the CSF is higher in pyogenic meningitis as compared to non-pyogenic meningitis and hence aids in the diagnosis of pyogenic meningitis.

Previous studies have also demonstrated that CSF-ADA estimation is useful in the diagnosis of TBM and can help to specifically identify tuberculous meningoencephalitis.

A combined analysis and comprehensive study is necessary to analyse their combined utility in the differentiation of the various forms of meningitis. Analysing the sensitivity and utility of these tests in our setup will improve management and care of patients with meningitis.

Aims and Objectives

1. To assess the utility of C-Reactive Protein and Adenosine Deaminase levels in differentiating the various forms of meningitis.

2. Establish a diagnostic cut off level for ADA in Cerebrospinal fluid in our setup.

Methods and Methodology

TYPE OF STUDY: A Prospective study design.

SOURCE OF DATA: Patients admitted to Department of Medicine of SDM College Medical Sciences and Hospital, meeting the inclusion criteria.

SAMPLE SIZE: 50 patients

STUDY POPULATION: Patients admitted under Department of Medicine meeting inclusion criteria.

STUDY DURATION: November 2014 to December 2015

INCLUSION CRITERIA: Patients of meningitis.

Criteria for diagnosis of meningitis:

Clinical symptoms of headache, fever, vomiting, altered sensorium and convulsions.

Examination findings -states of altered sensorium, signs of meningeal irritation, focal neurological deficits.

CSF analysis and Radiological findings favouring any form of meningitis.

Classification of the patients into the various forms of meningitis was done on the basis of clinical features and CSF analysis¹.

Exclusion Criteria:

1. Patients with acute infections at sites other than CNS.

2. Patients in whom lumbar puncture was contraindicated.

3. Age <18 years.

Statistical Analysis

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented as mean +/-SD and results on categorical measurements are presented in number.

Fischer extraction test has been used to find the significance of CRP and ADA levels in different types of meningitis.

Sensitivity, specificity, positive predictive value, negative predictive values were calculated to know the diagnostic performance of CRP and ADA.

Statistical Software

Statistical Software namely Statistical Package for Social Science and MedCalc were utilized. Microsoft Word and excel were utilized to make charts, graphs etc

Results

50 cases were selected for the study based on the inclusion and exclusion criteria during the study period.

Out of 50, 22 cases (44%) of the patients were diagnosed with tuberculous meningitis and 20 cases (40%) were diagnosed with viral meningitis. Only 6 (12%) cases were found to have pyogenic meningitis. Two cases were diagnosed to have fungal meningitis. Both of them had concurrent retroviral disease.

Types of Meningitis	No. of Cases	Percentage
Tubercular	22	44%
Viral	20	40%
Pyogenic	06	12%
Fungal	02	4%

The number of patients diagnosed with pyogenic meningitis were relatively fewer compared to tuberculous or viral meningitis which together constituted upto 84% of the cases.

CSF Adenosine Deaminase

The Mean value of ADA in different forms of meningitis was as follows:

Tuberculous Meningitis- 17 ± 8.5 IU/L

Viral Meningitis- 9.7 ± 3.3 IU/L

Pyogenic Meningitis- 11 ± 5.1 IU/L

Fungal Meningitis- 8.6 ± 1.8 IU/L

Other diagnostic Performance values of ADA using a diagnostic cut off of 10 IU/L

were as follows:

SENSITIVITY	86 %
SPESIFICITY	53 %
POSITIVE PREDICTIVE VALUE	59 %
NEGATIVE PREDICTIVE VALUE	83%

ADA levels were found to be elevated in CSF of patients with tuberculous meningitis.

This result was statistically significant with a p value of 0.003.

With respect to diagnostic performance values, a very low specificity and positive predictive value was found for ADA in our setup when a diagnostic cutoff of 10IU/L was used, however sensitivity was 86%.

CSF C –REACTIVE PROTEIN:

The mean value of CRP in different forms of meningitis was as follows:

Tuberculous Meningitis -0.92 ± 0.55 mg/L

Viral Meningitis -0.82 ± 0.5 mg/L

Pyogenic Meningitis $- 3.22 \pm 1.99$ mg/L

Fungal Meningitis -5.68 ± 4.02 mg/L

Other diagnostic performance values of CRP using an arbitrary diagnostic cutoff of

2mg/L were as follows:

Sensitivity	83 %
Specificity	95 %
Positive Predictive Value	71 %
Negative Predictive Value	95 %

CRP levels were found to be elevated in CSF of patients with pyogenic meningitis.

This result was statistically significant with a p value of 0.001.

With a cutoff value of 2mg/L, the sensitivity and specificity was 83% and 95% respectively, which is quite acceptable.

Incidentally CSF-CRP was also found to be elevated in the cases of fungal meningitis.

OPTIMAL Cutoff Value for ADA

One of the aims of our study was to establish an optimal cut-off value for ADA in our setup. A statistical methodology used for such analysis is ROC curve.

FIGURE 1— ROC Curve for Analysis of Optimal Cutoff

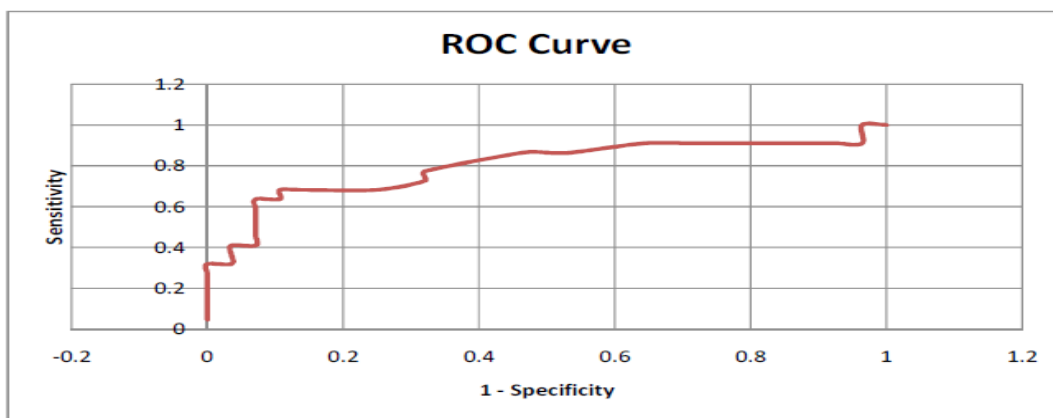


FIGURE 1— ROC Curve for Analysis of Optimal Cutoff

Based on analysis of the curve and based on tabular analysis, an optimal cut off value in our setup would be 12.9IU/l, with which one can obtain a sensitivity of 63.63% and specificity of 89.2%.

Discussion

Acute infections of the nervous system are emergencies in medicine. Distinguishing various types of meningitis requires lab parameters which are rapid, sensitive and specific and also cost effective.

CRP and ADA in CSF are two such widely studied parameters in this context. Some studies have shown utility of ADA in diagnosing tuberculous meningitis with varying sensitivity and specificity. Similarly, studies have also demonstrated the utility of CRP in differentiating pyogenic and non-pyogenic meningitis.

Testing these parameters at our centre would aid in assessing their utility and possibly improve management of patients with neuroinfection in the future.

Adenosine Deaminase

In our study 22 patients were diagnosed with Tuberculous Meningitis. The mean ADA value in these patients was 17 ± 8.5 IU/L (in patients diagnosed with TBM); 9.7 ± 3.3 IU/L in patients with pyogenic meningitis and 11 ± 5.1 U/L in viral meningitis. Compared to the other groups, the result was found to be statistically significant in the TBM group (p value-0.003).

With a cut off value of 10 IU/L used the sensitivity and specificity was found to be 86% and 63% respectively.

There was also a co-relation between the levels of ADA and the clinical picture. With elevated ADA levels there was worsening clinical picture, with complications such as hydrocephalus seen at levels >20 IU/L.

Multiple studies and meta-analyses have been done on the utility of ADA in CSF.

One of the larger **meta-analysis** on utility of CSF-ADA was conducted by **Xu H.B et.al**² where around 10 satisfactory studies which had evaluated CSF-ADA were analysed.

According to the met-analysis the mean values of sensitivity of ADA in the diagnosis of TBM as 79%, specificity 91%, positive likelihood ratio of 6.85 & negative likelihood ratio 0.29. Out of the 10 studies analysed three studies showed relatively low sensitivity (<0.70) and six studies demonstrated low specificity (<0.90) for the detection of ADA in diagnosing TBM.

In another **meta-analysis** on CSF-ADA by **FF Tuon.et.al**³ where up to 13 studies were analysed. The sensitivity, specificity and diagnostic odds ratio was calculated based on arbitrary cut-off values between 1 to 10IU/L. Based on analysis they however concluded that ADA cannot accurately distinguish between TBM and bacterial meningitis but using ranges would be important.

Multiple Indian studies done at various centres across India have also analysed the utility of ADA in diagnosing tuberculous meningitis.

TABLE 4 - COMPARISON OF STUDIES WHICH HAVE ANALYSED CSF-ADA

	Year of publication	Place of study	Cut off value	Sensitivity	Specificity
Amulya C Belagavi et.al ⁷	2011	Tumkur	10 IU/L	74 %	94 %
Ashok Agarwal et.al ⁸	2014	Patna	10 IU/L	87.5 %	83.3 %
Manoj Mathur et.al ⁹	2016	Allahabad	10 IU/L	76 %	85 %
Kashyap RS et.al ¹⁰	2006	Nagpur	11.4 IU/L	82 %	83 %
Raj R Sharma et.al ¹¹	2015	Gwalior	10 IU/L	75.5 %	100 %
Amol R Shinde et.al ¹²	2015	Nanded	10 IU/L	90 %	97 %

Thus, variable levels of sensitivity and specificity have been found in the various studies. In our study the sensitivity was acceptable, however specificity was much lesser than in other studies.

Probably, it would be ideal to compare the various studies with knowledge of the method of ADA analysis used also.

Certain studies such as *Chotmongkol.et.al⁴*, have tried to find a cut off value based on ROC analysis. Comparing the ADA activity between the tuberculous meningitis cases and nontuberculous meningitis cases the ROC curve identified a CSF ADA level of 15.5 U/l as the best cut-off value to differentiate between the two, with a sensitivity of 75% and a specificity of 93%. In a study by *HasanK.et.al⁵* the ADA activity cut-off level of 11 IU/L was advised for differential diagnosis of TB and non-tuberculous meningitis by applying ROC analysis, and its sensitivity was 92% and specificity was 90%.

Thus multiple studies have got reference values at their setup to achieve maximum specificity and sensitivity by applying an ROC analysis and most are in the range of 9-15IU /L. Using a similar analysis in our study, the cut-off in our setup would be 12.9IU/L

Therefore, similar to other studies our study also showed that ADA is useful in identifying and diagnosing tuberculous meningitis. However in view of low specificity obtained with a cut-off of 10IU/l caution may have to be exercised in diagnosing patients with TBM based on ADA alone.

A higher cut-off value may have to be utilized to improve the specificity. In view of its good sensitivity and negative predictive value the disease maybe

confidently ruled out if ADA is not elevated.

C-Reactive Protein

In our study 7 patients were diagnosed with pyogenic meningitis based on clinical, and CSF & radiological findings. The mean CRP value in patients diagnosed with pyogenic meningitis was 3.22 ± 1.99 mg/L; 0.92 ± 0.55 mg/L in patients with TBM; in those with viral meningitis was 0.82 ± 0.5 mg/L & in fungal meningitis was 5.68 ± 4.02 mg/L. With an arbitrary cut off value of 2mg/L, the sensitivity and specificity of CRP in our study was found to be 83% and 95% respectively.

Multiple studies done previously have demonstrated the utility of CRP in diagnosis of pyogenic meningitis, however with varying sensitivity & specificity. Of note is the fact that the CRP values obtained in studies which have used nephelometric techniques is different from those which have used pure latex agglutination & quantification techniques. We have utilized a nephelometry based technique in our study.

Meta-analyses on utility of CRP have been done many years ago. In a meta-analyses by *Gerdas Le et al⁶* where around 25 studies were analysed, it was estimated that the sensitivity and specificity was 94% and 60% respectively. Based on further analyses of the study they perceived that only a negative test is highly informative in a typical clinical setting and that it is difficult to conclude on the clinical usefulness of CRP tests in the management of patients suspected of having bacterial meningitis.

Multiple Indian studies have also been done at various centers across India which have analysed the utility of CRP in CSF. All of them have demonstrated

good sensitivity and specificity of CRP in the identification of pyogenic meningitis. India. (Table 5)

The results obtained in our study was comparable with that of other studies done over the past few years in

Thus, CSF-CRP assessed by nephelometry is a reliable indicator of pyogenic meningitis and can be used in rapid diagnosis of the same.

	Year of Publication	Place	Sensitivity	Specificity
Amulya C Belagavi et.al ⁷	2011	Tumkur	83.3 %	100 %
Anil Kumar T et.al ⁸	2010	Bengaluru	86 %	98 %
Raj R Sharma et.al ¹¹	2015	Gwalior	93.3 %	100 %
Amol R Shinde et.al ¹²	2015	Nanded	86.11 %	98.43 %
PRESENT STUDY		Dharwad	83 %	95 %

Thus, CSF-CRP assessed by nephelometry is a reliable indicator of pyogenic meningitis and can be used in rapid diagnosis of the same.

Conclusions

1. ADA in CSF is a good predictor of tuberculous meningitis. with good sensitivity but specificity of variable or questionable value

2. A cut off value of ADA in our setup of 12.9IU/L would probably improve positive predictive value and specificity of ADA in our setup. Similar analyses is probably required at every setup to identify an optimal value.

3. CRP levels are elevated in patients with pyogenic meningitis. Nephelometric techniques measure very small amounts of CRP too. This test which is not used routinely can be utilized for considering a diagnosis of pyogenic meningitis.

Limitations of the Study

1. A larger sample size would have probably yielded better results and conclusions.

2. Number of cases of pyogenic meningitis were relatively much lesser than that of viral and tuberculous meningitis. If more number of pyogenic meningitis were available, the utility of CSF- CRP would have been better studied.

3. Literature does not adequately compare studies based on the technique used for estimation of these parameters-ADA and CSF and whether differences in

technique would alter sensitivity or specificity of the test.

Ethical Clearance: obtained from ethical committee of SDM medical college and hospital, Dharwad.

Source of Funding: Self

Conflict of interest: Nil

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A Comparative Study of Clinical and Angiographic Profile of Acute Stemi Patients in Age Group of Below and Above 40 Years in South Indian Population

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Background: ACS-STEMI in young adults may have some characteristics such clinical, novel CVRF's & angiographic profile that are different from those in older patients.

Objective: To assess the frequency, risk factors, presenting symptoms, treatment in-hospital outcomes of young patients with STEMI compared with those of older patients

Material and Method: The present study had 242 cases of acute ST elevation MI of both the sex, aged below and above 40 years treated in Cardiology department. Risk factors including hsCRP, Lp(a) and homocystiene; presenting symptoms, in two age groups were analyzed.

Results: Acute ST elevation MI patients in age group below 40 years were 18.6% and in above 40 years age group were 81.4%. Overall mean age of presentation of STEMI is 54.31 years. STEMI was more common in younger age group 88.9% than in older age group 76.6%. STEMI was more common in male (78.9%) than female (21.1%). Overall most common symptom was breathlessness (72.3%), in younger age group chest pain was common (71.1%). The prevalence of hypertension and DM much or less equally distributed in both age groups. Prevalence of smoking in younger age group was 64.4% and in older age group 53.3%. A family history of CAD in younger age group was 35.6% and in older age group 24.9%. Lipoprotein (a) level was higher in younger age group which is statistically significant. hsCRP levels was increased above the normal range in older age group patients which was statistically significant.

Conclusion: Acute ST elevation MI patients in age group below 40 years were 18.6% and in above 40 years age group were 81.4%. Acute STEMI was more common in male than female. Most common symptom was breathlessness. Lipoprotein (a) was significantly higher in younger age group; hsCRP was significantly higher in older age group.

Key words – STEMI, ACS, Novel risk factors, HsCRP, Lipoprotien(a), Homocysteine, CAG

Introduction

The novel cardiovascular risk factors (CVRFs) like homocysteine (Hcy), lipoprotein(a) (Lp[a]), high-

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sensitivity C-reactive protein (hsCRP) are less well studied in Indian STEMI patients. The objective of this study was to represents the clinical profile, prevalence of risk factors and distribution of coronary artery stenosis in acute coronary syndrome (ACS) patients of South Indian population of age above and below 40 years.

Method

The present study comprised of 242 cases of acute ST elevation MI of both sexes, were analysed with