

## A STUDY OF CEREBROSPINAL FLUID, C-REACTIVE PROTEIN AND ADENOSINE DEAMINASE LEVELS IN MENINGITIS IN ADULTS

Katragadda Suneetha<sup>1</sup>, H. Vijaya Kumar<sup>2</sup>

<sup>1</sup>Assistant Professor, Department of General Medicine, Rangaraya Medical College, Kakinada, Andhra Pradesh.

<sup>2</sup>Associate Professor, Department of General Medicine, Rangaraya Medical College, Kakinada, Andhra Pradesh.

### ABSTRACT

#### BACKGROUND

Infectious disease remains a major cause of death and disability for millions around the world, in spite of progress in many antibiotics and preventive strategies. Even though, CNS is protected by blood brain barrier, a system of tight junction around capillaries fail to resist the entry of microorganisms at times. Its presence, prevents the achievement of sufficient concentration of antibiotics in CSF. CNS infections can cause devastating sequelae, and in some cases, it can present as neurological or medical emergencies.

#### MATERIALS AND METHODS

CSF samples were obtained from 50 patients of clinically suspected cases of meningitis who are admitted in Medicine Department of Government General Hospital, Kakinada, during the period from October 2013 and September 2016. A sample size of 50 patient were included in the study.

#### RESULTS

CRP levels were elevated in pyogenic meningitis. The mean CRP level in our study was  $30.2 \pm 5.22$  mg/dL. The patients with tuberculous and viral meningitis had a mean CRP level of  $2.37 \pm 4.79$  mg/dL and  $1.17 \pm 0.31$  mg/dL, respectively. In our study, we had high values of ADA in TBM with a mean of  $14.17 \pm 11.2$  U/L. In pyogenic meningitis, it was  $3.4 \pm 3.03$  U/L, and in viral meningitis, it was  $1.96 \pm 0.99$  U/L. Higher cutoff values for ADA helped in separating the overlapped cases of pyogenic and TBM.

#### CONCLUSION

As in previous studies, it is apparent from the results of our study that the level of ADA in CSF was considerably elevated in TBM compared with viral meningitis. This conclusion has proved to be extremely beneficial in the treatment of viral meningitis where patients have been started inadvertently on prolonged courses of antitubercular medication with the misdiagnosis of tubercular meningitis. We found that the ADA levels correlated with the severity of clinical presentation. Patients who presented with altered sensorium, cranial nerve involvement and hemiparesis were noted to have higher ADA values. However, there was no clear correlation with the outcome. One fatal case of tubercular meningitis had an ADA of 52 U/L (although, few patients with a mild elevation above the cut-off value have also died).

#### KEYWORDS

C-Reactive Protein, Adenosine Deaminase, Meningitis.

**HOW TO CITE THIS ARTICLE:** Suneetha K, Kumar HV. A study of cerebrospinal fluid, C-reactive protein and adenosine deaminase levels in meningitis in adults. *J. Evid. Based Med. Healthc.* 2017; 4(27), 1589-1594. DOI: 10.18410/jebmh/2017/310

#### BACKGROUND

Infectious disease remains a major cause of death and disability for millions around the world in spite of progress in many antibiotics and preventive strategies.

Even though, CNS is protected by blood brain barrier, a system of tight junction around capillaries fail to resist the entry of microorganisms at times. Its presence, prevents the achievement of sufficient concentration of antibiotics in CSF.

*Financial or Other, Competing Interest: None.*  
*Submission 01-03-2017, Peer Review 15-03-2017,*  
*Acceptance 21-03-2017, Published 31-03-2017.*

*Corresponding Author:*

*Dr. Katragadda Suneetha,*  
*Assistant Professor, Department of General Medicine,*  
*Rangaraya Medical College, Kakinada, Andhra Pradesh.*  
*E-mail: dr.hariyala20@gmail.com*  
*DOI: 10.18410/jebmh/2017/310*



CNS infections can cause devastating sequelae, and in some cases, it can present as neurological or medical emergencies.

#### Definition

Meningitis is an infection within the subarachnoid space. It is associated with a CNS inflammatory reaction that may result in decreased consciousness, seizures, varied intracranial pressure and stroke.<sup>1</sup>

Leptomeningitis indicates involvement of pia or arachnoid. It is also called pia-arachnitis.

Pachymeningitis indicates involvement of the dural layer of the meninges.

The meninges, subarachnoid space and brain parenchyma are all frequently involved in inflammatory process (meningoencephalitis).

### Acute Bacterial Meningitis

The annual incidence of bacterial meningitis is more than 4-6/1,00,000. Approximately, 1.2 million cases of bacterial meningitis occur annual worldwide with approximately 1,35,000 deaths. The disease is more common and the mortality is higher in developing countries like India.<sup>2</sup>

The use of biological markers like acute phase proteins and lymphokines has been proposed to facilitate the accuracy of the initial diagnosis. Today, CRP is the most widely available diagnostic test to differentiate bacterial meningitis from no bacterial, although it should be used only in conjunction with the clinical data.<sup>3</sup>

### Tuberculous Meningitis

Tuberculous meningitis is important cause of morbidity and mortality in India. Its medical emergency should be treated immediately. One should not wait for microbiological or molecular diagnostic confirmation. As the early diagnosis is the key for favourable outcome, failure to do so results in high morbidity and mortality. With the global epidemic of HIV, there is increasing incidence of both reactivated and newly-acquired infections. TBM is always secondary to TB somewhere else in the body. Extrapulmonary TB including CNS, TB is considerably more frequent in the setting of HIV infection than otherwise.

Adenosine deaminase levels have shown promising results in the diagnosis of tuberculosis infection of pleura, peritoneum, pericardium and meninges.

### Viral Meningitis

Viral meningitis is not a nationally reportable disease; however, it has been estimated that the incidence is about 75,000 cases per year. In tropical climates, there is a substantial increase in cases during the rainy season reflecting the seasonal predominance of enterovirus and arthropod-borne virus (arbovirus) infections.

### Clinical Presentation

Clinical presentation of meningitis varies. Seizures occur as part of the initial presentation of meningitis or during the course of the illness in up to 40% of patients. Raised Intracranial Pressure (ICP) is an expected complication of bacterial meningitis and is the major cause of obtundation and coma in this disease.<sup>4,5</sup>

### Aim of Study

Aim of this study is to evaluate whether C-reactive protein and adenosine deaminase levels could be used to differentiate the various types of meningitis in adults.

## MATERIALS AND METHODS

### Source of Data

CSF samples were obtained from 50 patients of clinically suspected cases of meningitis who are admitted in Medicine Department of Government General Hospital, Kakinada, during the period from October 2013 and September 2016.

A sample size of 50 patients were included in the study.

### Inclusion Criteria

- Age >18 years.
- Clinical features suggestive of meningitis.

### Exclusion Criteria

- Age <18 years.
- A patient with acute infections at sites other than central nervous system.
- Patients in whom lumbar puncture is contraindicated.
- Associated severe hepatic dysfunction.
- Severe dyslipidaemia.
- Patient on steroids.
- Patients with fungal meningitis.

### Criterion for Diagnosing Various Types of Meningitis

**Group 1-** This includes 5 cases of pyogenic meningitis based on clinical features usually acute in onset. It may be associated with otitis media, sinusitis and signs of meningeal irritation.

### CSF Analysis

- Pleocytosis of >250 cell/mm<sup>3</sup> predominantly neutrophils.
- Proteins >45 mg/dL.
- Sugar <40% of blood glucose concentration.
- Gram staining and culture positivity.
- Neuroimaging- Diffuse meningeal enhancement, abscesses or parameningeal focus.

**Group 2-** This include 36 cases of tuberculous meningitis based on-

Clinical features- usually insidious in onset, maybe associated with TB of other organs or signs of meningeal irritation.

### CSF Analysis

- Pleocytosis of >10 cells/mm<sup>3</sup>, predominantly lymphocytes.
- Protein >45 mg/dL.
- Sugar <40% of blood glucose concentration.
- Ziehl-Neelsen staining maybe positive for AFB.
- Neuroimaging- Meningeal enhancement, basal exudates and tuberculoma.

**Group 3-** This included 9 cases of viral meningitis based on clinical presentation, usually acute in onset with signs of meningeal irritation.

### CSF Analysis-

- Lymphocytic pleocytosis of >25 cells/mm<sup>3</sup>.
- Proteins >45 mg/dL.
- Sugar normal.
- Neuroimaging-diffuse meningeal enhancement.

### Calculations

The CRP concentration in the sample is calculated using the following formula-

$$\frac{(A2 - A1) \text{ Sample}}{(A2 - A1) \text{ Standard}} \times C \text{ Standard} = \text{Sample (mg/dl)}$$

**Estimation of ADA in CSF**

**Principle-** ADA hydrolyses adenosine to ammonia and inosine. The ammonia formed further reacts with phenol and hypochlorite in an alkaline medium to form blue indophenol complex with sodium nitroprusside acting as a catalyst. Intensity of the blue is proportional to the amount of ADA.

Adenosine + H<sub>2</sub> → Inosine + ammonia.  
 Ammonia + phenol + hypochlorite → Blue indophenols.

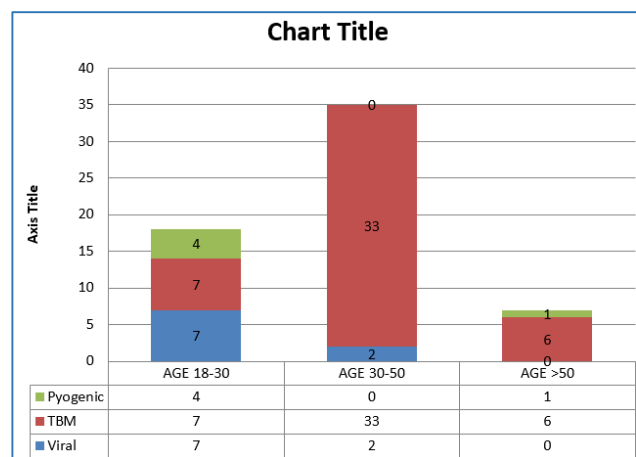
Study Design- A prospective clinical evaluation study is undertaken to study the predictive value of CRP and ADA in relation to various types of meningitis.<sup>6,7</sup>

**OBSERVATIONS AND RESULTS**

Type of Meningitis	Number	Percentage
Pyogenic meningitis	5	10
TBM	36	72
Viral meningitis	9	18
<b>Total</b>	<b>50</b>	<b>100</b>

**Table 1. Distribution of Types of Meningitis**

In our study, we have high case number of TBM, followed by viral and pyogenic. The percentage of TBM being 72%, viral 18%, pyogenic 10%.



**Age Distribution of Meningitis**

In our study, we had high incidence of TBM in the middle age. Pyogenic meningitis occurred more in the young adults.

Gender	Total Cases	Pyogenic	TBM	Viral
Male	40	4	31	5
Female	10	1	5	4
<b>Total</b>	<b>50</b>	<b>5</b>	<b>36</b>	<b>9</b>

**Table 2. Sex Distribution in Meningitis**

In our study, we had high incidence of TBM in males compared to females in pyogenic and viral meningitis. There was no much significant difference.

Type of Meningitis	Average Neutrophil Count/mm <sup>2</sup>
Pyogenic meningitis	238
TBM	4.5
Viral meningitis	4.3

**Table 3. Average Neutrophil Count in Meningitis**

In our study, the highest average neutrophil count is seen in pyogenic meningitis (238/mm<sup>3</sup>). TBM and viral meningitis had low levels of neutrophils.

Type of Meningitis	Average Lymphocyte Count/mm <sup>2</sup>
Pyogenic meningitis	3.2
TBM	67
Viral meningitis	30

**Table 4. Average Lymphocyte Count in Meningitis**

In our study, we had high average lymphocyte counts in TBM (67/mm<sup>3</sup>) followed by viral meningitis (30/mm<sup>3</sup>). Pyogenic had low levels of lymphocytes.

Type of Meningitis	No. of Cases	CRP (mg/dL)
Pyogenic	5	30.2 ± 5.22
TBM	36	2.43 ± 4.79
Viral	9	1.17 ± 0.31

**Table 5. Values of CRP in Various Types of Meningitis**

CRP levels were elevated in pyogenic meningitis. The mean CRP level in our study was 30.2 ± 5.22 mg/dL. The patients with tuberculous and viral meningitis had a mean CRP level of 2.37 ± 4.79 mg/dL and 1.17 ± 0.31 mg/dL, respectively.

Type of Meningitis	Number	ADA Levels (U/L)
Pyogenic	5	3.4 ± 3.03
TBM	36	14.17 ± 11.2
Viral	9	1.96 ± 0.99

**Table 6. ADA Levels in Various Types of Meningitis**

In our study, we had high values of ADA in TBM with a mean of 14.17 ± 11.2 U/L. In pyogenic meningitis, it was 3.4 ± 3.03 U/L and in viral meningitis, it was 1.96 ± 0.99 U/L. Higher cutoff values for ADA helped in separating the overlapped cases of pyogenic and TBM.

Type of Meningitis	No.	CRP (>20 mg/dL)	
		No. (%)	P Value
Pyogenic meningitis	5	5 (100%)	0.001
TBM	36	1 (2.7%)	-
Viral meningitis	9	-	-
<b>Total</b>	<b>50</b>	<b>6 (12%)</b>	

**Table 7. p Value of CRP**

In our study, all the cases of pyogenic meningitis have CRP values above the cut-off level, i.e. 20 mg/dL. Only 1 out of 36 case of TBM showed CRP levels more than the cut-off value. In viral meningitis, no case had positive CRP value.

	CRP +ve (>20 mg/dL)	CRP -ve (<20 mg/dL)
Pyogenic meningitis	5	0
Non-pyogenic meningitis	1	44

**Table 8. The Diagnostic Significance of CRP in Various Types of Meningitis**

If CRP value of 20 mg/dL is taken as cut-off for the diagnosis of pyogenic meningitis, the statistical indices are-

Sensitivity	---	100%
Specificity	---	97%
PPV	---	83%
NPV	---	100%
Accuracy	---	98%

Type of Meningitis	Number	ADA (>9 IU/dL)	
		No. (%)	P Value
Pyogenic meningitis	5	-	-
TBM	36	25 (69.4%)	0.007
Viral meningitis	9	-	-
<b>Total</b>	<b>50</b>	<b>25 (50%)</b>	-

**Table 9. p Value of ADA**

In our study, 69% of cases have shown ADA level above the cut-off level, i.e. 9 U/L. No cases of pyogenic or viral meningitis have positive ADA values.

	ADA +ve (>9 U/L)	ADA -ve (<9 U/L)
TBM	25	12
Non-TBM	1	12

**Table 10. Diagnostic Significance of ADA in Various Types of Meningitis**

If ADA level of 9 U/L is taken as cut-off for diagnosis for TBM the statistical indices are-

Sensitivity	---	67%
Specificity	---	92%
PPV	---	96%
NPV	---	50%
Accuracy	---	74%

**DISCUSSION**

Infections involving in CNS-like meningitis and encephalitis, which are not uncommon in our country, produce much anxiety in the patients and doctors. This is because of the high mortality rates associated with these conditions, if they are not diagnosed early and treated promptly and the high incidence of permanent sequelae that maybe seen even after the disease is cured. We began this study with the objective of using both ADA and CRP levels in CSF to differentiate various types of meningitis and to establish a cut-off level for ADA.

Adenosine deaminase is an enzyme involved in purine catabolism leading to hydrolysis and deamination of adenosine to inosine and ammonia. ADA has shown promising results in diagnosis of tuberculous pleural, peritoneal and pericardial effusion and tuberculous meningitis. C-reactive protein is a marker of acute phase

response or inflammation. Usage of CRP in differentiating pyogenic and non-pyogenic meningitis has been documented.<sup>8,9</sup>

**Adenosine Deaminase (ADA)**

CSF-ADA levels are raised in tuberculous meningitis and their use has been suggested to help in differentiating tuberculous meningitis from viral and bacterial meningitis.

Sang-Ho Choi et al studied ADA activity in CSF of 182 patients with meningitis. The mean ADA level in tuberculous meningitis 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 0.83 and 0.95, respectively when a cut-off value of 7 U/L was used.<sup>10</sup>

Pettersson et al reports sensitivity of 1.0 and specificity of 0.99 when a cut-off value of 20 U/L was used, but in that study, there were only 3 enrolled tuberculous meningitis patients.<sup>11</sup>

Chotmongkol V et al identified a CSF-ADA level of 15.5 U/L as the best cut-off value to differentiate tuberculous meningitis and non-tuberculous meningitis with a sensitivity of 75% and specificity of 93%. When tuberculous meningitis was compared with aseptic and carcinomatous meningitis, a CSF-ADA level of 19.0 U/L was the best cut-off value for differentiation with a sensitivity of 69% and a specificity of 94%.<sup>12</sup>

In our study, a total of 36 patients were diagnosed as tubercular meningitis based on the clinical features and CSF analysis. The mean ADA activity was 14.17 ± 11.2 U/L in the viral meningitis group. Comparing the ADA activity in the 3 groups, the difference was found to be statistically significant (p<0.05) in the tuberculous meningitis group compared to the other groups. The sensitivity and specificity was 67% and 92%, respectively when a cut-off value of 9 U/L was used.

Malan C et al showed in both bacterial and TBM groups, the mean ADA level in the CSF was significantly higher than in aseptic meningitis (p<0.001), but a significant difference was not shown between bacterial meningitis and TBM groups.<sup>13</sup> Similar results were noted in our study where the mean ADA value in viral meningitis was 1.96 ± 0.99 U/L, which was well below the cut-off value.

However, the value of ADA in the differential diagnosis of bacterial meningitis and fungal meningitis is controversial and there has been no cut-off value of CSF-ADA activity.<sup>14</sup>

In our study, we have found that the mean value of CSF ADA was 3.4 ± 3.03 U/L in pyogenic meningitis. Martinez et al reported that CSF-ADA activities were not significantly different between the group with tuberculous meningitis and the group with cryptococcal meningitis in AIDS patient. According to a study by Lopez, CSF-ADA levels were raised in cases of neurobrucellosis and cryptococcal meningitis.<sup>15</sup> It has been postulated that the selective increase of ADA depends on the degree of stimulation of T lymphocytes rather than the total numbers. Ena et al reported CSF-ADA elevation in tuberculous meningitis patients with significant T cell depleted AIDS.<sup>16</sup>

Gambhir et al found that the mean CSF-ADA levels in TBM patients was  $9.6 \pm 4.10$  U/L and was significantly elevated as compared to viral encephalitis cases, but the difference was insignificant in comparison to pyogenic meningitis and cerebral malaria.<sup>17</sup>

ADA exists as 2 isoenzymes, ADA-1 and ADA-2. It appears that ADA-2 isoenzyme originates mainly from monocytes and macrophages. ADA isoenzyme analysis by Schutte CM et al concluded that the ratio of ADA-2/ADA (total) was  $>0.8$  in patient with tuberculous meningitis.<sup>18</sup> The level of ADA-2 was tested in our study.

It has been suggested by Piras and Gakis that ADA levels in CSF may help differentiate TBM from viral meningitis and further that TBM and bacterial meningitis differ clearly from one another as regards the relationship ADA to the number of cells.<sup>19</sup>

As in previous studies, it is apparent from the results of our study that the level of ADA in CSF was considerably elevated in TBM compared with viral meningitis. This conclusion has proved to be extremely beneficial in the treatment of viral meningitis where patients have been started inadvertently on prolonged courses of antitubercular medication with the misdiagnosis of tubercular meningitis.

We found that the ADA levels correlated with the severity of clinical presentation. Patients who presented with altered sensorium, cranial nerve involvement and hemiparesis were noted to have higher ADA values. However, there was no clear correlation with the outcome. One fatal case of tubercular meningitis had an ADA of 52 U/L (although, few patients with a mild elevation above the cut-off value have also died).

The test for ADA in CSF is simple and can be carried out in a central laboratory with a rapid diagnosis, thus reducing unwarranted or harmful therapy for patients.

The finding of our study is that CSF-CRP is significantly higher in pyogenic meningitis compared to non-pyogenic meningitis. This result remained statistically significant with  $p < 0.05$ . The sensitivity and specificity of the test was 83.3% and 100%, respectively with accuracy of 98%.

Previous studies conducted by Goran Rajs et al have observed that CSF-CRP levels are higher in gram-negative pyogenic meningitis compared to gram-positive pyogenic meningitis suggesting that infection with gram-negative bacteria probably enhances permeability of CRF through the blood brain barrier.<sup>20</sup>

A recent meta-analysis by Gerdes LU et al suggested that a negative CRP test in either CSF or serum can be used with a very high probability to rule out bacterial meningitis.

In a study conducted by Vaishnavi C et al, CRP in CSF was significantly higher in patient with pyogenic meningitis compared to tuberculous meningitis. Authors conclude that the estimation of CRP in the differential diagnosis of meningitis might be made to give a preliminary diagnosis of meningitis.<sup>21</sup>

Riberio MH et al found that levels of CRP in CSF from 33 patients with bacterial meningitis, 21 patients with lymphocytic meningitis and 54 controls. In conclusion,

authors recommend that the estimation of CRP in CSF in the differentiation of bacterial from non-bacterial meningitis.<sup>22</sup>

Patients with hepatic dysfunction, dyslipidaemia, females on oral contraceptives and patients on steroids were not included in the study as each of these factors independently affect CRP levels.

## SUMMARY

Meningitis is the most common form of CNS infection, which occurs throughout the world. The initial treatment of meningitis is most of time presumptive. A number of recent studies strongly suggest that ADA activity in CSF is elevated in tuberculous meningitis. CSF-CRP levels can reliably discriminate between pyogenic and non-pyogenic meningitis. Thus, 2 rapid diagnostic tests. CSF-ADA activity and CRP levels can help in the differential diagnosis of tubercular, pyogenic and viral meningitis. However, they should be interpreted judiciously in the lights of the patients' clinical manifestations and the CSF characteristics. In our study, a total of 36 patients were diagnosed as tuberculous meningitis based on the clinical features and CSF analysis. The mean ADA activity was  $14.17 \pm 11.2$  U/L in the tuberculous meningitis group;  $3.4 \pm 3.03$  U/L in the pyogenic meningitis group;  $1.96 \pm 0.99$  U/L in the viral meningitis group. Comparing the ADA activity in the 3 groups, the difference was found to be statistically significant ( $p < 0.05$ ) in the tuberculous meningitis group compared to the other groups. The sensitivity and specificity was 67% and 92% respectively when a cut-off value of ADA of 9 U/L was used.

We found that CSF-CRP is significantly higher in pyogenic meningitis compared to non-pyogenic meningitis. This result remained statistically significant with  $p < 0.05$ .

The sensitivity and specificity of the test was 100% and 97%, respectively with an accuracy of 98%.

Most of the TBM patients were HIV positive patients with a proportion of about 44 in our study.

## CONCLUSION

1. CSF-ADA activity was higher in patients with tubercular meningitis when compared to pyogenic and viral meningitis.
2. CSF-CRP levels were higher in pyogenic meningitis than in non-pyogenic meningitis.
3. Both CRP and ADA levels are not raised in viral meningitis.
4. ADA can be used to assess the severity of TBM.
5. ADA levels did not correlate with the outcome of tubercular meningitis.

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