

## SIGNIFICANCE OF CEREBROSPINAL FLUID (CSF) C-REACTIVE PROTEIN (CRP) IN VARIOUS TYPES OF MENINGITIS

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### ABSTRACT

#### BACKGROUND

Meningitis often presents as a medical emergency which requires rapid and prompt diagnosis with aggressive management to select appropriate therapy to prevent mortality and long-term morbidity. Sometimes clinical signs and symptoms, results of routine CSF analysis and radiological findings are inadequate in making a definitive diagnosis of meningitis. On the other hand, tests like ELISA, Gram's and AFB stain of CSF are although rapid techniques for detection of organism, have disadvantages of cost, availability and sensitivity respectively. With GeneXpert, diagnosis of Mycobacterium tuberculosis and RIF resistance is now available in less than 2 hours but again has disadvantage of cost and availability. In such circumstances, the determination of CSF CRP appears to provide a new dimension to the additional supportive diagnosis of the type of meningitis.

#### METHODS

The study was carried out on 90 patients admitted in the Department of Medicine, Gauhati Medical College & Hospital, Guwahati, Assam. The final diagnosis of the type of meningitis was based on the clinical criteria, biochemical, cytological & bacteriological examination of CSF.

#### RESULTS

In our study, the mean CRP in CSF of patients with bacterial meningitis, tubercular meningitis and viral meningitis were 24.00±11.17 mg/dl, 5.27±3.15 mg/dl and 2.57±3.11 respectively. The calculated p values show that the difference is statistically significant ( $p < 0.0001$ ) when the means of bacterial group is compared with the other two.

#### CONCLUSION

CSF CRP level can be used to differentiate bacterial meningitis from tubercular and viral meningitis.

#### KEYWORDS

CRP, Meningitis, Cerebrospinal Fluid.

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#### BACKGROUND

Infections of the nervous system are amongst the most important problem in medicine with considerable morbidity and mortality. Meningitis is one such clinical syndrome characterized by inflammation of meninges. The classical triad of meningitis consists of fever, headache and neck stiffness. The causes of meningitis may be broadly classified as infectious (bacterial, viral, fungal) and non-infectious (cancer-related, systemic lupus erythematosus, drug induced, head trauma, and brain surgery). The most

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common types of meningitis are bacterial meningitis (BM), tubercular meningitis (TBM) and viral meningitis.<sup>1</sup>

The etiologic diagnosis of meningitis remains a problem in clinical practice as CSF biochemical analysis & cellular response often overlap. Thus, there is a need of rapid diagnosis of aetiology of meningitis for better patient outcome as accurate initial diagnosis is the corner stone for therapeutic decision making of acute meningitis. Meningitis is still a very common and serious disease. Death is not uncommon and many who survive are left permanently disabled. Thus, meningitis which often presents as a medical emergency which requires rapid and prompt diagnosis with aggressive management to select appropriate therapy to prevent mortality and long-term morbidity associated with the disease. Delay in distinguishing bacterial from other infections of central nervous system may have irrevocable consequence as the regenerative capacity of central nervous tissue is limited and hence prompt and correct diagnosis to select appropriate therapy is required. Distinguishing the aetiologies also helps in terms of both reducing antibiotic

usage and hospital bed occupancy and reassuring contacts of cases.<sup>2</sup>

Although many diagnostic modalities are available with the advancement of time, sometimes signs and symptoms, results of routine CSF analysis and radiological findings are inadequate to arrive at a definitive diagnosis of the type of meningitis due to various loopholes associated with the different diagnostic procedures. The CSF analysis and culture still remains the most useful method for diagnosis of meningitis but the patients in whom CSF analysis for Gram's stain and culture are negative there is no other test definitive for or against diagnosis of bacterial meningitis. For example, Gram's stain and AFB stain of CSF are rapid technique for detection of organism but lack sensitivity. ELISA although helpful but are costly, not easily available and not easily performed. With introduction of Gene Xpert, a highly specific and sensitive test it is now possible to detect Mycobacterium tuberculosis and RIF resistance in less than two hours but has again the similar disadvantages of being costly and not widely available. In such circumstances, a number of test measuring levels of various CSF protein, enzymes and mediators- including ADA, C-reactive protein,<sup>3</sup> lactic acid,<sup>4</sup> lactate dehydrogenase,<sup>5</sup> YKL-40,<sup>6</sup> quinolinate,<sup>7</sup> Interleukins like IL-1beta, IL-6, soluble IL-2 receptor,<sup>8,9</sup> beta 2 microglobulin and ferritin,<sup>10</sup> procalcitonin<sup>11</sup> and TNF<sup>12</sup> etc. has been proposed.

C-reactive protein is an acute phase reactant of "Pentraxin" group of family. It is synthesized exclusively in liver and is secreted in large quantities within 6 hours of an acute inflammatory stimulus in serum or fluids associated with the affected tissues. Raised CSF CRP level in meningitis is due to passive diffusion across the highly inflamed meninges. Hence, increased serum CRP levels signify acute phase response, thus increased CSF CRP signifies meningeal involvement. CSF CRP testing appears to be an attractive option for rapid diagnosis of bacterial meningitis and hence many studies have been done to evaluate this role of CSF CRP. But there is still conflicting data regarding the use of this test and it has yet to become a standard part of the meningitis diagnostic battery. Many of the previous studies in relation to CSF CRP & meningitis have used a Qualitative CRP assay.<sup>13</sup>

The final diagnosis of the types of meningitis was based on clinical criteria and biochemical, cytological and bacterial examination of CSF analysis.

### Aims and Objectives

1. To estimate C-reactive protein (CRP) level along with other diagnostic parameters in cerebrospinal fluid of patients with meningitis.
2. To evaluate whether CRP level could be used to differentiate the various types of meningitis.

## METHODS

### Study Design

This was a hospital based observational study.

### Study Place

Study was conducted in the Department of Medicine, Gauhati Medical College & Hospital, Guwahati, Assam

### Study Duration

One year from 1<sup>st</sup> June 2017 to 31<sup>st</sup> May 2018.

### Sample Size

Ninety (90) patients

### Inclusion Criteria

- Age of 12 years or greater of either gender.
- Patients who are clinically suspected as meningitis and later confirmed with lumbar puncture and subsequent CSF analysis.

### Exclusion Criteria

- Age less than 12 years.
- Patients in whom lumbar puncture was contraindicated.
- Patients with severe hepatic failure.
- Patients who have received antibiotics before presenting to the hospital.
- Patients who are found to have fungal meningitis or meningitis other than bacterial, tubercular or viral aetiologies from clinical, laboratory or imaging studies.

All patients who fulfilled the inclusion criteria of the study underwent a physical examination and neurological assessment on admission and when not contraindicated immediate lumbar puncture (LP) was performed prior to the first dose of antibiotics. Initial cerebrospinal fluid (CSF) analysis for all patients included microscopy, white cell count and differential, protein and glucose levels, Gram stain and culture, India ink stain, and CSF fungal antigen test. Repeat Lumbar puncture (LP) procedure for CSF analysis was performed when necessary. Apart from CSF analysis additional investigations which were performed are bacterial culture and antibiotic susceptibility testing. Computed tomography (CT) scanning of the head was performed in some, but not all patients with focal neurological deficits and/or altered mental status prior to lumbar puncture or within 24-48 hours of admission to exclude intracranial space occupying lesions and other causes of raised intracranial pressure. Patients with clinical suspicion of TB meningitis and/or HIV infection underwent sputum acid fast bacilli (AFB) smear and culture testing and chest radiography to screen for the presence of TB. Routine biochemical investigations for all patients included full blood count, liver function tests, and urea and electrolytes. Clinical, radiological, microbiological, and other laboratory data were evaluated, and the diagnosis of meningitis was made based on a combination of clinical and CSF findings (CSF protein and glucose levels, cell count and differential, microscopy, and culture) as explained below.

**Diagnostic Criteria of Different Types of Meningitis<sup>14</sup>**

**Bacterial Meningitis**

Bacterial meningitis was diagnosed based on a positive CSF Gram stain and/or culture. In patients without a definitive microbiological diagnosis, bacterial meningitis was diagnosed when patients had a compatible clinical presentation and typical CSF findings (CSF pleocytosis with polymorphonuclear cell predominance, low glucose, and elevated protein).

Patient’s response to antibiotic therapy was closely monitored.

**TB Meningitis**

A diagnosis of TB meningitis was made when patients had clinical features of meningitis with negative CSF Gram stain and cultures for bacteria, negative CSF fungal antigen test and at least one of the following:

- (i) characteristic CSF findings (CSF pleocytosis with lymphocytic predominance, low glucose, and elevated protein);
- (ii) CSF CBNAAT positive.
- (iii) brain CT findings suggestive of TBM such as basal meningeal enhancement or hydrocephalus.
- (iv) Patients showing resolution of constitutional symptoms within 14-21 days of starting anti-TB treatment.

**Viral Meningitis**

Viral meningitis was diagnosed when Patients had clinical features of meningitis with negative CSF Gram stain and cultures for bacteria, negative for CSF fungal antigen test, and typical CSF findings (CSF lymphocytic predominance, normal or slightly elevated protein, and normal glucose) with exclusion of non-viral causes of aseptic meningitis and/or CSF polymerase chain reaction (PCR) for viral pathogens positive.

**RESULTS**

- 1) In this study, out of 90 patients, the age ranged from 13 to 85 years and mean age was 39.92±17.71 years. Majority 37(41.11%) were in the age group of 21-40 years followed by 31 (34.44%) in 41-60 years. While there were 11 patients (12.22%) in the age group 12-20 years and similar number of patients of > 60 years.

Age Group	No. of Patients	Percentage
12-20	11	12.22%
21-40	37	41.11%
41-60	31	34.44%
>60	11	12.22%

**Table 1. Showing Age Distribution of Cases of Meningitis**

- 2) In the present study, out of 90 patients 52(57.78%) were male and 38(42.22%) were female. The male to female ratio was 1.39:1.

Sex	No. of Patients (n=90)	Percentages
Male	52	57.78%
Female	38	42.22%
Total	90	100%

**Table 2. Showing Sex Distribution of Cases of Meningitis**

- 3) In this study, out of 90 patients, viral meningitis (n=38; 42.22%) was the most common aetiology, followed by tubercular meningitis (TBM) (n=33; 36.67%). Bacterial meningitis constitutes 21.11% (n=19) cases.

Aetiology	No. of Patients (n=90)	Percentage
Bacterial	19	21.11%
Tubercular	33	36.66%
Viral	38	42.22%
Total	90	100

**Table 3. Distribution of Various Types of Meningitis**

- 4) In this study the mean CSF CRP was 8.02+10.04 with value ranging from 0 to 42 mg/L. Mean CSF CRP in bacterial group was 24.00± 11.17. The mean CSF CRP in tubercular meningitis was 5.27±3.15 and in viral group 2.57±3.11. The calculated p values showed that the difference is statistically very highly significant (p<0.0001) when the means of bacterial group is compared with the other two.

Aetiology	Mean CSF CRP
Bacterial	24.00±11.17
Tubercular	5.27±3.15
Viral	2.57±3.11

**Table 4. Level of CSF-CRP in Different Meningitis**

- 5) Case Distribution on the basis of the type of Meningitis & CSF CRP Level

In the viral meningitis group, most of the cases (86.84%) and in TBM 51.52% cases have CRP level less than 5 mg/L. In comparison bacterial meningitis group have none case in less than 5 mg/L group but have value more than 20 mg/L.

**DISCUSSION**

C reactive protein can help in differentiating bacterial from tubercular and viral meningitis. Large number of studies conducted around the world suggests that CRP levels in the CSF are higher in bacterial meningitis compare to tubercular or viral meningitis and hence aid in the differential diagnosis and management of meningitis.

In our study, the mean CRP in CSF of patients with bacterial meningitis, tubercular meningitis and viral meningitis were; 24.00±11.17 mg/dl, 5.27±3.15 mg/dl and 2.57±3.11 mg/dl respectively. The finding of our study is that CSF-CRP is significantly higher in bacterial meningitis compare to tubercular and viral meningitis. The calculated p values showed that the difference is statistically very highly significant (p<0.0001) when the means of bacterial group is compared with the other two. However, the difference between the means of Viral & TB group was found to be statistically insignificant (p>0.05).

A meta-analysis by Gerdes LU et al and Sutinen J 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 which is consistent with the results of our study.<sup>15</sup>

These findings are similar to those of the other studies mentioned below-

In the study by Belagavi et al, which calculated the mean CSF CRP in different aetiology was as follows 27.00±13 in bacterial meningitis, 1.09±0.3 in TBM and 1.12±0.48 in viral meningitis. Likewise, in our study also CSF CRP value for bacterial aetiology was found to be higher than the other two.<sup>3</sup>

Jain, S et al, in their study found that the mean CRP were 32.50±2.03 in bacterial meningitis cases, 1.54±0.2 in tubercular meningitis cases, and viral meningitis cases value were 2.42±0.36. Statistically significantly higher value was observed with bacterial meningitis cases compared to TBM and VM cases ( $p < 0.001$ ) which is similar to the results of our study.<sup>16</sup>

Aharwar S et al, in their study the mean CSF CRP levels in bacterial, tuberculous and viral groups were calculated and compared. In this study also the bacterial meningitis group had a mean level of 16.223 mg/L, which is much higher as compared to the mean levels in other two groups (2.244 mg/L in TB meningitis group and 0.875 mg/L in viral meningitis group.<sup>13</sup> This study correlates with the findings of our study.

Malla, K.K et al in 2013 found that CSF CRP was 45.75 in bacterial meningitis, 1.20 in tubercular meningitis and 4.44 in viral meningitis. Therefore, the results of this study correlate with the results of our study as well.<sup>17</sup>

## CONCLUSION

In the present study, we found that CSF CRP level is significantly higher in bacterial meningitis patients as compared to that in tubercular and viral meningitis patients. CSF analysis is an important diagnostic tool to differentiate bacterial from tubercular and viral meningitis. Furthermore, considering the diagnostic limitation of conventional CSF variables (protein, glucose and cells) especially when Grams/AFB stain and culture are negative, the CSF CRP can provide pertinent, rapid and reliable diagnostic information and is very useful in distinguishing bacterial from tubercular and viral meningitis. However, further studies with larger sample size may be needed to arrive at a definite conclusion.

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