

## CSF C-Reactive Protein in Meningitis

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### Abstract

**Background:** Meningitis is defined as an infection involving the subarachnoid space. It may be associated with inflammatory process of the central nervous system (CNS) leading to a decreased level of consciousness, seizures or raised intracranial pressure. CNS is protected by the blood brain barrier (BBB) which resists the entry of pathogens, inflammatory cells, and macromolecules into the subarachnoid space. The BBB may be breached in the presence of infections leading to meningitis. The aetiological diagnosis of meningitis is a diagnostic dilemma. Usually, non specific indicators like CSF glucose, protein concentration, WBC or neutrophil count are used for aetiological diagnosis of meningitis. CSF C-reactive protein (CRP) levels can prove to be a rapid and simple method for specific diagnosis of meningitis. CSF CRP levels in meningitis are raised due to passive diffusion across the inflamed meninges. Normally, CRP is present in trace amounts (< 0.5 mg/dl) in the plasma and in negligible amounts in the CSF.

**Material and method:** The study was a hospital-based cross-sectional study carried-out from 1st January 2018 to 30th June 2019 in a tertiary care hospital of North India. Total of 110 patients were enrolled for the study. Routine blood and CSF investigations were sent along with CSF CRP and lactate levels.

**Results:** Mean CSF CRP levels were significantly higher in bacterial meningitis ( $3.08 \pm 1.95$  mg/dl) as compared to other types of meningitis ( $p = 0.005$ ). CSF CRP levels were significantly higher in patients with Thwaites' score > 4 ( $p = 0.03$ ) and in patients with BM-CASCO score  $\geq 3$  ( $p = 0.00001$ ).

**Conclusion:** CSF CRP levels can help in differentiating bacterial meningitis from other types of meningitis.

**Key words:** Meningitis, cerebrospinal fluid, C-reactive protein.

### Introduction

Meningitis is defined as infection predominantly involving subarachnoid space, associated with CNS inflammatory process leading to decreased or loss of consciousness, seizures, and raised intracranial pressure<sup>1</sup>. Meningitis is a significant cause of morbidity and mortality worldwide. Without adequate treatment the case fatality rate can be as high as 70 per cent, and one in five survivors of meningitis may be left with permanent sequelae including hearing loss or any other neurological disability. Neurological outcome and survival depends largely on damage to central nervous system prior to effective antimicrobial therapy. Quick diagnosis and effective management is the key to success<sup>2</sup>. The aetiological diagnosis of meningitis is a diagnostic dilemma. The cerebrospinal fluid (CSF) biochemical analysis and cellular response overlap in various conditions. In patients with bacterial meningitis, CSF culture and sensitivity is the most reliable method, which is positive in 30 - 60% cases only and requires at least 48 to 72 hours to be positive<sup>3</sup>. Usually non-specific indicators like CSF glucose, chloride, protein level, and WBC or neutrophil count are used for aetiological diagnosis of meningitis. Therefore, CSF C-reactive protein

(CRP) levels can prove to be a rapid and simple method for specific diagnosis of meningitis. C-reactive protein (CRP) is an acute phase reactant of "Pentraxin" group of family<sup>4</sup>. Within 6 hours of an acute inflammatory stimulus, CRP is exclusively produced by hepatocytes and secreted in serum or fluids associated with involved tissues. Tillett *et al* discovered CRP and acute phase inflammatory response in 1930<sup>5</sup>. CSF CRP levels in meningitis are raised due to passive diffusion across inflamed meninges. Normally CRP is present only in trace amount in plasma (< 0.5 mg/dl) and is negligible in CSF. In acute infection, serum CRP concentration can rise up to 3,000 mg/dl within 24 to 48 hours. The concentration of CSF CRP is raised in meningitis<sup>2</sup>. This study is designed to evaluate the diagnostic role of CSF CRP in clinically diagnosed cases of meningitis.

### Aims and objectives

1. To study the diagnostic significance of cerebrospinal fluid CRP in evaluation of bacterial meningitis.
2. Correlation of CSF CRP levels with BM – CASCO and Thwaites' scores.

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## Material and methods

This study is a hospital-based cross-sectional study conducted in a tertiary care hospital of North India. All patients with clinical diagnosis of meningitis over a period of 18 months were included in the study and subjected to lumbar puncture after informed consent. Routine blood and CSF investigations were sent. CSF was sent for microbiological (cytology, Gram's stain, culture and sensitivity, TB-PCR, Z-N stain) and biochemical (protein, sugar, lactate, ADA, and CRP) analysis. CSF CRP levels were estimated using Beckman Coulter CRP - latex reagent kit on its full automated instrument AU 480.

Sample size: 110 patients.

### Inclusion criteria

All patients above the age of 18 years with clinical diagnosis of meningitis were included in the study after informed consent.

Thwaites' and BM-CASCO scores were calculated for all patients and correlated with the CSF CRP levels.

### Thwaites' diagnostic scoring<sup>5</sup>

Parameters	Cut-off values	Score
Age (years)	≥ 35 < 35	20
Blood WBC (10 <sup>3</sup> /ml)	≥ 15,000 < 15,000	40
History of illness (days)	≥ 6 < 6	-50
CSF total WBC (10 <sup>3</sup> /ml)	≥ 900 < 900	30
CSF neutrophils %	≥ 75 < 75	40

### Bacterial meningitis – careggi score (BM-CASCO)<sup>6</sup>

Blood/CSF parameters	Cut-off values	Score
CSF cell count (cells/ul)	≤ 50 > 50	02
CSF protein (mg/dl)	≤ 80 > 80	01
CSF lactate (mg/dl)	≤ 35 < 35	01
CSF glucose/serum glucose ratio (%)	≥ 45 < 45	01
Peripheral neutrophil count (cells/ul)	≤ 10,000 ≤ 10,000	01

### Statistical analysis

A cross-sectional study was carried-out on 110 patients of meningitis. These patients were divided into the following groups: Bacterial meningitis, Tubercular meningitis, Viral meningitis, Scrub typhus meningitis and Paraneoplastic meningitis based on clinical and CSF findings. Data was entered using Microsoft Office Excel and were analysed by appropriate statistical methods including tests of significance using SPSS (Statistical Packages for Social

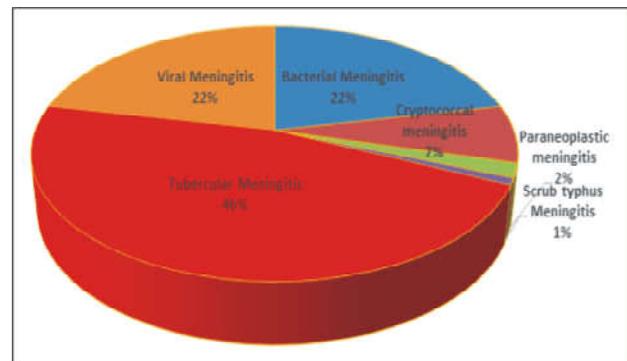
Sciences, version 21.0. Armonk, NY: IBM corp). Quantitative data was reported as means and standard deviations wherever necessary. Categorical variables were classified as frequency of occurrence and were analysed by using Chi-square test or ANOVA t-test. A p value of < 0.05 was considered significant.

## Results and analysis

Total of 110 patients of meningitis were admitted over the period of eighteen months with male preponderance (58.2%). Fever (100%) and headache (80%) were the commonest presenting symptoms (Table I).

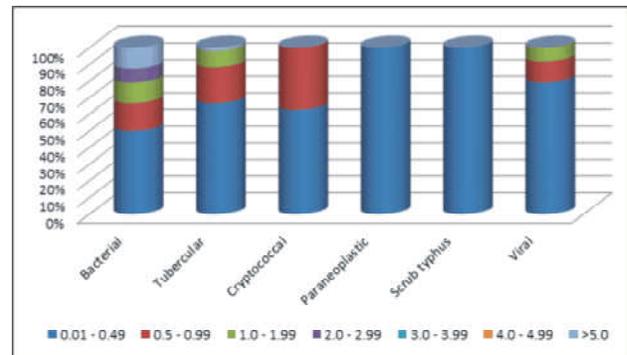
**Table I:**

Symptom	Frequency (n = 110)	Percentage
Fever	110	100
Headache	88	80
Vomiting	55	50
Seizures	43	39.1
Loss of consciousness	14	12.7



**Fig. 1:** Aetiological spectrum of meningitis.

There were 51 cases of tubercular meningitis, 24 cases of viral and bacterial meningitis each, 8 cases of cryptococcal meningitis, 2 cases of paraneoplastic meningitis and 1 case of Scrub typhus meningitis.



**Fig. 2:** CSF CRP in various type of meningitis.

CSF CRP levels were found to be below 0.5 mg/dl in 73 (66.3%) patients. Only 4 (3.6%) patients were found to have CSF CRP value > 5 mg/dl. Highest levels of CSF CRP (> 5 mg/dl) were found in 3 (12.5%) patients with bacterial meningitis and 1 (1.96%) patient with tubercular meningitis. mean CRP levels were found to be highest in bacterial meningitis (Fig. 3). This result was found statistically significant (p = 0.005).

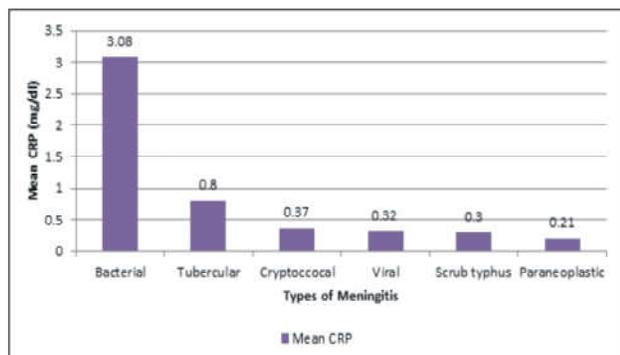


Fig. 1: Mean CRP.

48 (43.6%) patients had BM-CASCO  $\geq 3$  whereas 62 (56.4%) patients had BM-CASCO < 3. When CSF CRP values were correlated with BM-CASCO score, patients having score < 3 were found to have mean CSF CRP value of  $0.35 \pm 0.31$  mg/dl. However, patients with BM-CASCO score  $\geq 3$  were found to have higher values of mean CSF CRP ( $2.04 \pm 1.12$  mg/dl). This result was found to be statistically significant with p value of 0.00001 (Table II).

**Table II: Correlation between BM – CASCO scores and mean CSF CRP levels.**

BM CASCO score	N = 110	Mean CSF CRP (mg/dl)
< 3	62	$0.35 \pm 0.31$
$\geq 3$	48	$2.04 \pm 1.12$

87 (79.1%) patients were found to have Thwaites' score  $\leq 4$ . When Thwaites' score was correlated with mean CSF CRP levels, patients having Thwaites' score > 4 were found to have higher mean CSF CRP levels ( $2.53 \pm 2.29$  mg/dl) as compared patients having Thwaites' score  $\leq 4$  with mean CSF CRP level of  $0.26 \pm 0.19$  mg/dl. This is statistically significant with p value of 0.031.

**Table III: Correlation between Thwaites' score and mean CSF CRP levels.**

Thwaites' score	N = 110	Mean CSF CRP (mg/dl)
$\leq 4$	87	$0.26 \pm 0.19$
> 4	23	$2.53 \pm 2.29$

## Discussion

In our study, 110 patients were included with male preponderance (58.2%). Fever (100%) and headache (86%) were the commonest presenting symptoms and vomiting was seen in 55 (50%) patients, followed by seizures and loss of consciousness in 43 (39.1%) and 14 (12.7%) patients respectively. In this study, 51 cases of tubercular meningitis, 24 cases of viral and bacterial meningitis each, 8 cases of cryptococcal meningitis, 2 cases of paraneoplastic meningitis and 1 case of Scrub typhus meningitis were there.

Highest levels of CSF CRP (> 5 mg/dl) were found in 3 (12.5%) patients with bacterial meningitis and 1 (1.96%) patient with tubercular meningitis. Mean CRP levels were found to be significantly higher in bacterial meningitis ( $3.08 \pm 1.95$  mg/dl) as compared to  $0.32 \pm 0.28$  mg/dl in viral meningitis,  $0.80 \pm 0.52$  mg/dl in tubercular meningitis,  $0.37 \pm 0.36$  mg/dl in cryptococcal meningitis, 0.30 mg/dl in Scrub typhus meningitis and  $0.21 \pm 0.13$  mg/dl in paraneoplastic meningitis. This result remained statistically significant with p value = 0.005 (calculated by ANOVA test).

In this study, 87 (79.1%) patients were found to have Thwaites' score  $\leq 4$ . When Thwaites' score was correlated with mean CSF CRP levels, patients having Thwaites' score > 4 were found to have higher mean CSF CRP levels ( $2.53 \pm 2.29$  mg/dl) as compared patients having Thwaites' score  $\leq 4$  with mean CSF CRP level of  $0.26 \pm 0.19$  mg/dl. This difference is statistically significant with p value of 0.031. Hence, Thwaites' score of > 4 can be correlated with higher mean CSF CRP values and bacterial meningitis.

There were 48 (43.6%) patients with BM-CASCO score  $\geq 3$ . When CSF CRP values were correlated with BM-CASCO score, patients having score < 3 were found to have mean CSF CRP value of  $0.35 \pm 0.31$  mg/dl. However, patients with BM-CASCO score  $\geq 3$  were found to have higher values of mean CSF CRP ( $2.04 \pm 1.12$  mg/dl). This result was found to be statistically significant (p value 0.00001). Hence, BM-CASCO score of  $\geq 3$  can be correlated with higher CSF CRP values and bacterial meningitis.

Prashanth *et al* reported that mean CRP level in CSF of patients was 31.44 mg/dl, 0.86 mg/dl and 1.01 mg/dl in bacterial, tubercular and viral meningitis respectively<sup>7</sup>. Aharwar reported CSF CRP levels above 10 mg/dl in 26 (86.6%) cases of bacterial meningitis. Majority of cases (91.6%) of tubercular meningitis had a CSF CRP range of < 5 mg/dl and one case in range of 10 - 15 mg/dl. Likewise, all cases in viral meningitis group had CSF CRP in the range < 5 mg/dl<sup>8</sup>. Kumar conducted a study at MS Ramaiah Medical College, Bengaluru and mean CSF CRP level was found to be significantly higher in the pyogenic meningitis group

(28.88 mg/l), compared to the non-pyogenic meningitis (1.84 mg/l) and control groups (0.15 mg/l) which was statistically significant ( $p < 0.0001$ )<sup>9</sup>. Similar results were obtained by Belagavi in a study conducted at Tumkur. CRP levels were elevated in pyogenic meningitis. The mean CRP level was  $33 \pm 5.0$  mg/dl. The patients with tubercular and viral meningitis had a mean CRP level of  $1.09 \pm 0.3$  and  $1.12 \pm 0.48$  respectively<sup>10</sup>. Thwaites reported the sensitivity and specificity for prediction of tubercular meningitis as 95.8 and 71.6% respectively, but for patients with positive bacterial result confirmed by microscopy and/or culture evidence of bacteria in CSF the predictive values for sensitivity and specificity were 91.7 and 79.7%, thereby making Thwaites' diagnostic score a useful technique for differential diagnosis of tubercular meningitis. Patients with score  $\leq 4$  were classified as having tubercular meningitis and with score  $> 4$  were classified as non-tubercular or bacterial meningitis<sup>5</sup>. A study conducted by Lagi during a four-and-a-half year period (2010 - 2014) in tertiary care hospital in Italy reported that all acute bacterial meningitis cases showed a BM-CASCO  $\geq 3$ . Most negative cases exhibited BM-CASCO value of  $\leq 1$  which was further adopted in the laboratory as a cut-off to not proceed with urgent microbiological analysis of CSF in cases of suspected acute bacterial meningitis in adults. Hence, BM-CASCO score appeared to be an accurate and simple scoring system for optimisation of microbiological diagnosis of acute bacterial meningitis in adults<sup>6</sup>.

## Conclusion

CSF CRP can be used as biochemical marker of bacterial meningitis. CSF CRP levels can be correlated with BM-CASCO and Thwaites' scores to reach the diagnosis of bacterial meningitis.

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