



E-ISSN: 2706-9575  
P-ISSN: 2706-9567  
IJARM 2020; 2(2): 236-239  
Received: 22-05-2020  
Accepted: 25-07-2020

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## Role of C-reactive protein in neuroinfection

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**DOI:** <https://doi.org/10.22271/27069567.2020.v2.i2d.74>

### Abstract

CRP belongs to the pentraxin family of calcium dependent ligand-binding plasma proteins. The pentraxin family named for its electron micrographic appearance from the Greek penta (five), ragas (berras). CRP can be produced in neurons and lipopolysaccharides can induce CRP production in extrahepatic sites. Its production is controlled by interleukin-6 and it binds to polysaccharides present in many bacteria, fungi and protozoal parasites. Meningitis patients admitted and willing to give consent in the medicine department at Victoria hospital and Bowring & Lady Curzon hospital, BMCRI, Bangalore. The NPV was 100%, which implied that bacterial meningitis could be ruled out if the CSF-CRP was negative. The accuracy of CRP for bacterial meningitis was 100%.

**Keywords:** C-reactive protein, neuroinfection, pentraxin

### Introduction

The central nervous system (CNS) may appear protected from perturbations in the environment by a blood brain barrier - a system of tight junction around capillaries that resist the entry of pathogens, inflammatory cells and macromolecules into the subarachnoid space and the brain. However, the barrier fails to resist the intensity of the microbial world and its presence also cause difficulty in the delivery of antimicrobial agents in adequate concentrations<sup>[1]</sup>.

Bacterial meningitis is the most common form of suppurative CNS infection, with an annual incidence in the United States of >2.5 cases/100,000 population. The organisms most often responsible for community-acquired bacterial meningitis are *Streptococcus pneumoniae* (~50%), *Neisseria meningitidis* (~25%), group B streptococci (~15%), and *Listeria monocytogenes* (~10%). *Haemophilus influenzae* type b accounts for <10% of cases of bacterial meningitis in most series. *N. meningitidis* is the causative organism of recurring epidemics of meningitis every 8 to 12 years<sup>[2]</sup>.

A critical event in the pathogenesis of meningitis is the inflammatory reaction induced by the invading pathogen. Many of the neurologic manifestations and complications of meningitis result from the immune response to the invading pathogen rather than from direct bacteria induced tissue injury. As a result, neurologic injury can progress even after the CSF has been sterilized by antibiotic therapy<sup>[2]</sup>.

The prognosis of bacterial meningitis is critically dependent on a rapid causal diagnosis and implementation of prompt treatment. However, clinical and biochemical parameters available within the few hours that follow patients admission are not reliable enough, except when bacteria are to be found in the cerebrospinal fluid under the microscope. Today, C-reactive protein (CRP) is the most widely used inflammatory marker in emergency departments with aim to discriminate bacterial from non-bacterial infections<sup>[3]</sup>.

### C-reactive protein

Tillet and Francis, French investigators in 1930 described a substance that was present in the sera of acutely ill patients which was able to bind to the cell wall c-polysaccharide of *streptococcus pneumoniae* and agglutinate the organisms. In 1941, the substance was shown to be a protein and given the name C-reactive protein (CRP)<sup>[4]</sup>.

CRP belongs to the pentraxin family of calcium dependent ligand-binding plasma proteins. The pentraxin family named for its electron micrographic appearance from the Greek penta (five), ragas (berras)<sup>[5]</sup>.

CRP can be produced in neurons<sup>[6]</sup> and lipopolysaccharides can induce CRP production in

extrahepatic sites [7]. Its production is controlled by interleukin-6 and it binds to polysaccharides present in many bacteria, fungi and protozoal parasites [7].

In view of such observations, the present study was conducted to find out the usefulness of CSF-CRP for the rapid diagnosis & management of bacterial meningitis in adults.

## Methodology

### Source of data

Meningitis patients admitted and willing to give consent in the medicine department at Victoria hospital and Bowring & Lady Curzon hospital, BMCRI, Bangalore.

### Method of collection of data

This group included 50 Patients with clinical and CSF laboratory findings consistent with Bacterial meningitis.

### Clinical features

- Acute onset of symptoms of meningitis - Triad of fever, headache, nuchal rigidity.
- Altered mental status.
- Nausea, vomiting and photophobia.
- Seizures.
- Signs of meningeal irritation. Can be associated with sinusitis, otitis media, and signs of meningeal irritation.

### CSF analysis showing

- Pleocytosis of  $> 250$  cells/mm<sup>3</sup>, predominantly neutrophils.
- Proteins  $> 50$ mg/dl.
- Sugar  $< 40$ mg/dl.
- Gram stains and culture positivity.

### Neuroimaging showing

Evidence of diffuse meningeal enhancement, abscesses or parameningeal focus.

### Inclusion criteria

1. Age  $> 18$  years.
2. Clinical features suggestive of meningitis

### Exclusion criteria

1. Age  $< 18$  years.
2. Patients in whom lumbar puncture is contraindicated.
3. Associated severe hepatic dysfunction.
4. A patient with acute infections at sites other than central nervous system.
5. Patients on steroid.

An estimation of CSF C-Reactive protein level was done for all the patients satisfying the inclusion and exclusion criteria.

### Study design

A prospective clinical evaluation study is undertaken to study the predictive value of CSF CRP in relation to Bacterial meningitis.

### Statistical methods

Student t test (two tailed, independent) has been used to find

the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. LevenIs test for homogeneity of variance has been performed to assess the homogeneity of variance.

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented in Mean SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance.

### Significant figures

+ Suggestive significance ( $P$  value:  $0.05 < P < 0.10$ )

\* Moderately significant ( $P$  value:  $0.01 < P < 0.05$ )

\*\* Strongly significant ( $P$  value:  $P < 0.01$ )

### Statistical software

The Statistical software namely SAS 9.2, SPSS 15.0, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

## Results

**Table 1:** Age distribution of patients

| Age (Years) | Number of patients | In percentage (%) |
|-------------|--------------------|-------------------|
| 18-20       | 04                 | 8                 |
| 21-40       | 12                 | 24                |
| 41-60       | 29                 | 58                |
| $> 60$      | 05                 | 10                |
| Total       | 50                 | 100               |

The mean age of the 50 patients studied was  $39.86 \pm 14.58$  years. 58% (n=29) of patients in the study were aged between 41-60 years.

**Table 2:** Gender distribution of meningitis

| Gender | Bacterial meningitis | Percentage (%) |
|--------|----------------------|----------------|
| Male   | 31                   | 62%            |
| Female | 19                   | 38%            |
| Total  | 50                   | 100            |

In this study, 62% were Male and 38% were Female.

**Table 3:** Levels of CSF-CRP

| Type of meningitis   | Total number of patients | CRP (mg/dl)<br>Mean value $\pm$ SD |
|----------------------|--------------------------|------------------------------------|
| Bacterial meningitis | 50                       | $23.16 \pm 5.56$                   |

The mean CSF-CRP level in Bacterial meningitis, was  $23.16 \pm 5.56$  mg/dl.

**Table 4:**  $P$  value of CSF-CRP in bacterial meningitis

| Type of meningitis   | Total number of patients | CSF-CRP level ( $> 5$ mg/dl) |                |                   |
|----------------------|--------------------------|------------------------------|----------------|-------------------|
|                      |                          | Number                       | Percentage (%) | $P$ Value         |
| Bacterial meningitis | 50                       | 50                           | 100            | $P < 0.001$<br>** |

The result is statistically significant with a  $P$  value  $< 0.001$ .

**Table 5:** Diagnostic performance of CSF-CRP

| Type of meningitis   | Total number | Sensitivity | Specificity | PPV | NPV  | Accuracy |
|----------------------|--------------|-------------|-------------|-----|------|----------|
| Bacterial meningitis | 50           | 99%         | 100%        | 99% | 100% | 100%     |

The NPV was 100%, which implied that bacterial meningitis could be ruled out if the CSF-CRP was negative. The accuracy of CRP for bacterial meningitis was 100%.

### Discussion

The epidemiology of bacterial meningitis has changed

significantly in recent years reflecting a dramatic decline in the incidence of meningitis due to *Haemophilus influenzae*, and a smaller decline in that due to *Neisseria meningitidis*, following the introduction and increasingly widespread use of vaccines for both these organisms [1].

**Table 6:** Cerebrospinal fluid (CSF) abnormalities in bacterial meningitis [2]

|                     |   |
|---------------------|---|
| Opening pressure    | >180 mmH <sub>2</sub> O   |
| White blood cells   | 10 – 10,000/microLit; neutrophils predominate   |
| Red blood cells     | Absent in nontraumatic tap  |
| Glucose             | <2.2 mmol/L (<40 mg/dl)   |
| CSF/Serum glucose   | <0.4  |
| Protein             | >0.45g/L (>45mg/dl)   |
| Gram's stain        | Positive in >60%  |
| Culture             | Positive in >80%  |
| Latex agglutination | May be positive in patients with meningitis due to <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>Haemophilus influenzae</i> type b, <i>Escherichia coli</i> , Group B streptococci |
| Limulus lysate      | Positive in cases of gram-negative meningitis   |
| PCR                 | Detects bacterial DNA   |

**Abbreviation:** PCR– polymerase chain reaction

### Pathophysiology [2]

The most common bacteria that cause meningitis, *S. pneumoniae* and *N. meningitidis*, initially colonize the nasopharynx by attaching to nasopharyngeal epithelial cells. Bacteria are transported across epithelial cells in membrane-bound vacuoles to the intravascular space or invade the intravascular space by creating separations in the apical tight junctions of columnar epithelial cells. Once in the bloodstream, bacteria are able to avoid phagocytosis by neutrophils and classic complement-mediated bactericidal activity because of the presence of a polysaccharide capsule. Bloodborne bacteria can reach the intraventricular choroid plexus, directly infect choroid plexus epithelial cells, and gain access to the CSF. Some bacteria, such as *S. pneumoniae*, can adhere to cerebral capillary endothelial cells and subsequently migrate through or between these cells to reach the CSF. Bacteria are able to multiply rapidly within CSF because of the absence of effective host immune defenses. Normal CSF contains few white blood cells (WBCs) and relatively small amounts of complement proteins and immunoglobulins. The paucity of the latter two prevents effective opsonization of bacteria, an essential prerequisite for bacterial phagocytosis by neutrophils. Phagocytosis of bacteria is further impaired by the fluid nature of CSF, which is less conducive to phagocytosis than a solid tissue substrate.

A critical event in the pathogenesis of meningitis is the inflammatory reaction induced by the invading pathogen. Many of the neurologic manifestations and complications of meningitis result from the immune response to the invading pathogen rather than from direct bacteria induced tissue injury. As a result, neurologic injury can progress even after the CSF has been sterilized by antibiotic therapy [2].

Raised ICP is an expected complication of bacterial meningitis and the major cause of obtundation and coma in this disease. More than 90% of patients will have a CSF opening pressure >180 mmH<sub>2</sub>O, and 20% have opening pressures >400 mmH<sub>2</sub>O. Signs of increased ICP include a

deteriorating or reduced level of consciousness, papilledema, dilated poorly reactive pupils, sixth nerve palsies, decerebrate posturing, and the Cushing reflex (bradycardia, hypertension, and irregular respirations) [2].

The most disastrous complication of increased ICP is cerebral herniation. The incidence of herniation in patients with bacterial meningitis has been reported to occur in as few as 1% to as many as 8% of cases [2].

The rash of meningococemia begins as a diffuse erythematous maculopapular rash resembling a viral exanthem, but the skin lesions of meningococemia rapidly become petechial. Petechiae are found on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles [2].

This increase in CRP level might be due to entry of CRP into CSF by passive diffusion across the highly inflamed meninges or *de-novo* synthesis in central nervous system [8]. Present study was consistent with the findings of various studies.

In a study conducted by Vaishnavi C *et al*, CRP in CSF was significantly higher in patients with pyogenic meningitis compared to tubercular meningitis. Authors concluded that the estimation of CRP in the differential diagnosis of meningitis might be made to give a preliminary diagnosis of meningitis [9].

Riberio MH *et al* estimated the levels of CRP in CSF from 33 patients with bacterial meningitis, 21 patients with lymphocytic meningitis and 54 controls. 100% of these patients with bacterial meningitis were correctly classified on the basis of measurement of CRP levels in CSF. In conclusion authors recommend the estimation of CRP in CSF in the differentiation of bacterial from non-bacterial meningitis [10].

Hemavani V *et al* evaluated the role of CRP in CSF in differentiation of meningitis. The study included 499 CSF samples from cases of viral, pyogenic, tuberculous and fungal meningitis and 580 normal CSF samples. CRP positive by qualitative latex agglutination test was seen in

73.3% of CSF samples from partially treated pyogenic meningitis and 92% among pyogenic meningitis cases. All suspected cases of tuberculosis meningitis were negative for CRP in the CSF while only 1 out of CSF samples for bacteriologically confirmed tuberculous meningitis was positive. CRP was raised in 27.2% and 12.5% of CSF samples from candidal and cryptococcal meningitis cases respectively, while none of the 102 samples from suspected viral meningitis and 580 non-meningitis cases were positive for CRP in the CSF. The study concludes that CSF CRP determination can be of value to differentiate pyogenic versus other microbial meningitis etiology. However, it cannot differentiate between tuberculosis, fungal and viral meningitis<sup>[13]</sup>.

A 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<sup>[11, 12]</sup>.

### Conclusion

Study concludes that use of CSF C-Reactive Protein can be used for early diagnosis of Bacterial meningitis. This is necessary when gold standard test for meningitis like Smear and/or culture for bacteria, is not available or negative or time consuming.

CSF-CRP levels were higher in Bacterial meningitis.

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