# Cerebrospinal fluid C-reactive protein - A point of care test in the diagnosis of bacterial meningitis

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## ABSTRACT

**Background:** Bacterial meningitis is a significant life-threatening illness during infancy and childhood. Delay in distinguishing bacterial from viral or other aseptic meningoencephalitis may have irrevocable consequences. A typical case of pyogenic meningitis without prior antibiotics may not create any diagnostic problems, but prior treatment with inappropriate and inadequate antibiotics may cause sufficient alteration in biochemistry and cytology of cerebrospinal fluid (CSF), and organisms may not get isolated from blood or CSF culture. Objective: C-reactive protein in CSF (CSF-CRP) has been reported to be one of the most reliable and early indices to differentiate bacterial from non-bacterial meningitis. This study was undertaken to evaluate the diagnostic significance of CSF- CRP as an early indicator in the differentiation of bacterial from non-bacterial meningitis. Materials and Methods: This descriptive study was done in children in the age group of 1 month to 12 years who were admitted with history and clinical features suggestive of acute central nervous system infection. CSF was analyzed for macroscopic appearance, pleocytosis, proteins, and sugar content, Grams and Ziehl–Neelsen stain, and bacterial and mycobacterial culture. Qualitative assessment of CRP was done by slide latex agglutination method. Results: A total of 50 children each with culture-positive and culture-negative CSF were recruited. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of CSF-CRP for diagnosis of bacterial meningitis were 82%, 100%, 100%, 84.5%, and 91%, respectively. Conclusions: CSF- CRP can be reliably used as a point of care test in the bedside diagnosis of bacterial meningitis.

**Key words:** *Bacterial meningitis, Cerebrospinal fluid - C reactive protein, Point of care test*

Bacterial meningitis is an important cause of morbidity and mortality in children. The clinical features range from nonspecific symptoms such as irritability, fever, and refusal of feeds to specific features such as seizures, meningeal signs and neurological deficits. The case-fatality rate in bacterial meningitis can be as high as 30%, and one in five survivors have neurological sequelae such as deafness and cognitive dysfunction [1,2].

As the clinical presentation is protean and case fatality rate is high, a high index of suspicion is essential for early diagnosis and prompt institution of the meningitic dose of antibiotics for a better outcome. The gold standard for diagnosing bacterial meningitis is the culture of cerebrospinal fluid (CSF) ideally taken before antibiotic therapy. The other features are CSF pleocytosis, increased CSF protein content and hypoglycorrhachia. These parameters are not reliable enough to distinguish bacterial from other causes of central nervous system (CNS) infection or inflammation. Poor diagnostic yield of cultures due to prior antibiotic use and prolonged time for culture reports necessitate antibiotic coverage for all patients on a presumptive basis.

Moreover, all these investigations can be done only in places where round the clock laboratory facilities are available. Hence, a test which can be done at the bedside, does not require laboratory support and technical expertise, gives immediate results and most importantly, one that is not influenced by prior antibiotic therapy is the need of the hour. Obtaining immediate results will also help to avoid unnecessary prolonged antibiotic therapy in patients without bacterial meningitis; thereby, permitting judicious use of our limited resources.

C-reactive protein (CRP) is an acute phase reactant present in trace amounts in the blood of healthy individuals. CRP is elevated in all bacterial infections within a few hours of onset of inflammation and peaks in 24–48 h. It is not altered by prior antibiotic therapy. CRP is said to reach the CSF by diffusion through the inflamed meninges. A few studies have reported the utility of estimation of CSF-CRP levels in the diagnosis of pyogenic meningitis. Hence, this study was done to assess the CSF-CRP status in pyogenic meningitis and to compare with the gold standard, i.e., CSF culture. The sensitivity, specificity, and positive and negative predictive values of CSF-CRP were studied.

## METHODOLOGY

This descriptive study was conducted at a tertiary care teaching hospital in Tamil Nadu. The study was commenced after clearance

from the Institutional Ethics Committee. Written informed consent was obtained from parents. The sample size calculation was done with sensitivity/specificity of 98%, precision of 4%, and confidence level (CI) of 95%. A sample size of 47 was derived. Hence, 50 children were included in the study.

All children in the age group of 1 month to 12 years who got admitted to our hospital with history and clinical features suggestive of acute CNS infection, namely, fever, irritability, convulsions, vomiting, bulging fontanelle, and meningeal signs were included in the study. Those who were previously treated before hospitalization with intravenous antibiotics were excluded. Use of oral antibiotics was not considered for exclusion as most children had received them before hospitalization.

Detailed history and clinical examination including anthropometry were done. CNS examination including fundoscopy was performed, and findings were recorded in the pro forma. Relevant laboratory investigations including complete blood counts, blood culture, renal, and liver function tests were done. Children who underwent CSF analysis before the initiation of antibiotics were recruited for the study. CSF was analyzed for macroscopic appearance, cell count (total and differential), proteins, and sugar content (concomitant blood sugar was taken). Microbiological investigations, namely, Gram stain, Ziehl–Neelsen stain, and bacterial and mycobacterial culture were done.

Qualitative assessment of CRP was done by slide latex agglutination method. One drop of CSF was placed in the well of a standard testing plate given by the manufacturer using a disposable pipette to which was added a drop of CRP reagent (a uniform suspension of polystyrene latex particle coated with agglutinating sera for CRP. The reagent is standardized to detect CRP concentration >0.6 mg/dL according to the WHO reference preparation). The test specimen and CRP reagent are uniformly mixed over the entire well using a mixing stick. The plate is rocked gently back and forth and observed for agglutination macroscopically at the end of 2 min. CRP was taken as positive if agglutination occurred at the end of 2 min. Positive and negative controls were included for each of the CSF CRP tests.

All cases were managed as per the standard treatment protocol followed in our hospital. Based on CSF culture report, the study population was divided into two groups - culture-positive study group and culture-negative control group. Cases were recruited till there were 50 cases with culture-positive and 50 with culture- negative. Culture-negative group included children without bacterial meningitis (febrile seizures, viral, and aseptic meningitis). The two groups were compared and analyzed on the basis of demographic characteristics, clinical symptoms, and signs and CSF parameters. The CSF-CRP results were compared between the two groups.

Statistical analysis: Unpaired t-test was used for comparing mean difference between groups. SPSS version 16.6 (SPSS Inc, Chicago, IL, USA) was used for all statistical analysis and $p<0.05$ was taken as significant.

## RESULTS

The mean age of children in CSF culture-positive and culture-negative groups was 29 and 33 months, respectively, and was statistically similar (p=0.08; standard deviation = 0.9569). There was also no difference in the sex distribution between the groups (p=0.94) (Table 1).

Presenting symptoms of fever (p=0.0002), persistent vomiting (p=0.0039), and ALOC (p=0.0001) were significantly associated with culture-positive bacterial meningitis. Among the clinical signs, the presence of meningeal signs, circulatory shock, persistent ALOC, and papilledema was significantly associated with pyogenic meningitis (Table 1). The cytology, biochemistry (elevated protein and low glucose), and qualitative CRP were compared in both the groups (Table 2).

The most common organisms isolated in cases with pyogenic meningitis were *klebseilla* followed by *Escherichia coli* and *pseudomonas*. CSF-CRP was positive in 41 cases (82%) of culture-positive case (Table 3).

Sensitivity was 82% (95% CI - 68.56%–91.42%), specificity was 100% (95% CI - 92.89%–100.00%), positive predictive value was 100.00%, negative predictive value was 84.75% (95% CI - 75.46%–90.94%), and diagnostic accuracy was 91.00% (95% CI - 83.60%–95.80%). Chi-squared equals 66.143 with 1° of freedom. The two-tailed p value is <0.0001. The association between CSF-CRP and culture positivity is considered to be extremely statistically significant. The sensitivity and specificity

**Table 1: Epidemiological and clinical features of study and control groups**

| Characteristic | n=50 | | p value |
|---|---|---|---|
| | Study group (%) | Control group n (%), | |
| Age group | | | |
| 1 month–1 year | 25 (50) | 25 (50) | 1.0000 |
| 1–3 years | 13 (26) | 9 (18) | 0.3367 |
| 3–6 years | 8 (16) | 11 (22) | 0.4467 |
| 6–12 years | 4. (8) | 5 (10) | 0.7281 |
| Sex | | | |
| Male | 26 (52) | 27 (54) | 0.8420 |
| Female | 24 (48) | 23 (46) | 0.8420 |
| Symptoms | | | |
| Fever | 44 (88) | 27 (54) | 0.0002 |
| Headache | 9 (18) | 3 (6) | 0.0662 |
| Vomiting | 17 (34) | 5 (10) | 0.0039 |
| Seizures | 45 (90) | 44 (88) | 0.7505 |
| Altered sensorium | 46 (92) | 24 (48) | 0.0001 |
| Signs | | | |
| Meningeal signs | 23 (46) | 8 (16) | 0.0013 |
| Bulging AF* | 5 (10) | 1 (2) | 0.0938 |
| Shock | 23 (43) | 4 (8) | 0.0001 |
| ALOC# | 48 (96) | 20 (40) | 0.0001 |
| Focal neurological deficit | 19 (38) | 10 (28) | 0.2900 |
| Papilledema | 6 (12) | 1 (2) | 0.0512 |

*Anterior Fontanelle, #Altered level of consciousness

of abnormal biochemistry and polymorphic pleocytosis were compared with the CSF-CRP both individually and as a combination (Table 4).

## DISCUSSION

The etiological diagnosis of meningitis remains a problem as the clinical and biochemical picture is often masked because of prior antibiotic use. This is pronounced in a referral center like ours where children have already received parenteral antibiotics for a variable period of time before referral. Moreover, CSF cultures for pyogenic organisms are positive in only 30–60% of cases according to various researchers [3]. In many places, facilities for blood and CSF cultures are lacking and even if available, the time needed to get report hampers the use of culture as a bedside test even though it is the proven gold standard. CRP is normally present as a trace constituent of plasma (0.8 mg/dL) while it is negligible in CSF. The concentration of CSF-CRP is raised in patients with meningitis which can be detected by latex agglutination test at the bedside.

**Table 2: CSF analysis - macroscopic appearance, pleocytosis, biochemistry, and CRP**

| CSF | n=50 | | p value |
|---|---|---|---|
| | Study group (%) | Control group (%) | |
| Color | | | |
| Clear | 35 (70) | 50 (100) | 0.0001 |
| Turbid | 12 (24) | 0 (0) | 0.0002 |
| Purulent | 3 (6) | 0 (0) | 0.0802 |
| CSF cells | | | |
| Polymorphs | 25 (50) | 1 (2) | <0.0001 |
| Lymphocytes | 3 (6) | 3 (6) | 1.0000 |
| Nil | 22 (44) | 46 (92) | <0.0001 |
| Elevated proteins | 35 (70) | 10 (20) | <0.0001 |
| Hypoglcorrachia | 20 (40) | 10 (20) | 0.0299 |
| CSF-CRP positive | 41 (82) | 9 (18) | <0.0001 |

CSF: Cerebrospinal fluid, CRP: C-reactive protein

**Table 3: Comparison of CSF CRP analysis with culture**

| CSF Parameter | Culture positive | Culture negative |
|---|---|---|
| CRP | | |
| Positive | 41 | 0 |
| Negative | 9 | 50 |

CSF: Cerebrospinal fluid, CRP: C-reactive protein

In both the study and control groups, infants were most frequently affected, which has been observed in other studies too. This shows that both bacterial and non-bacterial meningitic involvement is common in infancy, thereby increasing our dependency on investigations for differentiation [4]. Fever, vomiting, and altered sensorium were the significant complaints in the study group, whereas seizures were present equally in both the groups. A similar observation was also recorded by other authors [5-7].

Most of the CSF samples (35%) in the culture-positive group were clear on gross appearance. Gross appearance is thus a very poor indicator of bacterial meningitis Although CSF pleocytosis favors culture-positive meningitis, 44% of them were acellular. This may be probably due to pre-hospital antibiotic usage or inadvertent delay in CSF processing which may cause desiccation of cells. In a study by Águeda *et al*., CSF pleocytosis had a sensitivity and specificity of 81% [8]. Hypoglycorrhachia was twice as common in our study group than the control group though the difference was not statistically significant. Hypoglycorrhachia in the control group may be due to cases of mumps or tuberculous meningoencephalitis.

There are varied reports about the sensitivity of CSF-CRP in predicting bacterial meningitis. Corral *et al.* found that CRP was elevated in the CSF of all the 24 patients with culture-proven bacterial meningitis but in only 2 of 32 patients with non-bacterial meningitis [9,10]. In our study, CSF-CRP was positive in 41 (82%) of the culture-positive cases with a sensitivity of 82% and 100% specificity. Hence, if CSF-CRP is positive, it virtually makes a diagnosis of bacterial meningitis irrespective of other investigations. For pyogenic meningitis, a sensitivity of 84% and 94%, and a specificity of 100% have been reported by other researchers. However, Abramson *et al*. had observed a higher sensitivity (97%) and lower specificity (86%) [11].

The highlight of our study is the observation of 100% specificity, i.e., the ability to detect true negatives. For the clinician, this is strategically important as this means that bacterial meningitis can be ruled out at the bedside if the CSF-CRP is negative. A similar view was also expressed by Gerdes *et al*., in his meta-analysis on 35 published articles on the diagnostic accuracy of CRP in CSF and serum to diagnose bacterial meningitis [12]. According to Corral *et al*., CSF-CRP is a more sensitive test for differentiating bacterial from non-bacterial meningitis than any other laboratory test for CSF. The positive likelihood ratio (LR) for CSF-CRP and bacterial meningitis was infinite meaning that if the CSF-CRP is positive, pyogenic meningitis is definitely present. There are

**Table 4: Comparison of sensitivity and specificity of various lab parameters in the diagnosis of bacterial meningitis**

| CSF Parameter | n=50 | | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|
| | Culture positive | Culture negative | | |
| Abnormal biochemistry | 37 | 10 | 74 (59.66–85.37) | 80 (66.28–89.97) |
| Polymorph pleocytosis | 25 | 1 | 50 (35.53–64.47) | 98 (89.35–9.95) |
| Abnormal CSF cytology+abnormal biochemistry | 40 | 11 | 80.00 (66.28–89.97) | 78.00 (64.04–88.47) |
| Abnormal CSF cytology+abnormal biochemistry+positive CRP | 45 | 12 | 90.00 (78.19–96.67) | 76.00 (61.83–86.94) |

CSF: Cerebrospinal fluid, CRP: C-reactive protein, CI: Confidence interval

no studies evaluating LR ratio for CSF CRP as far as we have searched in literature.

The limitations of our study were the inability to do a quantitative assessment of CRP and the inability to exclude children who had received oral antibiotics.

## CONCLUSION

Our study shows that CSF-CRP is a valuable investigation for prompt and accurate bedside diagnosis of bacterial meningitis. In developing countries like ours where case-load is high, coupled with lack of trained workforce and state-of-the-art labs and need to ration resource, this investigation will definitely be an asset to the clinicians. It will also be an asset to the health system at large by avoidance of unnecessary antibiotic usage and prolonged hospital stay.

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