

Raised C-Reactive Protein In Cerebrospinal Fluid: A Diagnostic Marker Of Bacterial Meningitis

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Abstract

Objective: To establish diagnostic role of CSF C-reactive protein quantitatively in meningitis.

Method: This prospective study was done on 50 patients. According to serum & CSF analysis 28 cases had pyogenic meningitis 22 cases had aseptic meningitis. Along with other appropriate investigations, quantitative CSF C-reactive protein (CRP) was assayed and data were analysed to set a diagnostic level and sensitivity and specificity of CSF –CRP in meningitis. **Result:** The differences in the mean values were statistically significant for CSF protein levels, CSF leukocyte count, and CSF/serum glucose between bacterial and aseptic meningitis groups ($p < 0.001$). Values of serum CRP had significant difference in bacterial meningitis group compared to other group ($p < 0.001$).

Conclusion: CSF CRP can easily differentiate bacterial meningitis from other meningitis with great sensitivity and specificity.

Keywords: CSF C-reactive protein (CRP), Meningitis.

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I. Introduction

Meningitis is inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges. The inflammation may be caused by infection with viruses, bacteria, or other microorganisms, and less commonly by certain drugs^[1].

In all forms of meningitis, the two major factors which lead to a poor outcome, are the state of consciousness of the patient on arrival in hospital and any delay in starting appropriate treatment. Delay in distinguishing bacterial from viral meningitis or meningoencephalitis may have irrecoverable consequences^[2].

A typical case of pyogenic meningitis without prior antibiotics may not create any diagnostic problem, 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^[3]. Moreover cerebrospinal fluid culture for pyogenic organisms are positive in only 30-60% of cases according to various Indian workers^[4]. Hence a quick and reliable method is required for bedside diagnosis.

A number of tests measuring levels of various CSF proteins, enzymes, and mediators—including C-reactive protein, lactic acid, lactate dehydrogenase, neopterin, quinolate, IL-1, IL-6, soluble IL-2 receptor, β_2 -microglobulin, and TNF—have been proposed as potential discriminators between viral and bacterial meningitis but different studies have shown different results^{[5][6]}.

C-reactive protein (CRP), an acute phase serum protein is a globulin formed by the body in response to various non-specific stimuli such as infection, tissue necrosis or neoplasm. Microbial infection stimulates hepatocytes in liver to produce CRP. Serum CRP has been reported to be useful in differential diagnosis & monitoring the clinical course of the meningitis. Serum CRP level returns to normal within 7 days in patients with uncomplicated bacterial meningitis^[7].

Plenty number of patients are admitted with clinical diagnosis of meningitis, encephalitis and local suppuration in this hospital. It is difficult to distinguish them without further investigations. Moreover, as discussed above, bacterial meningitis pose a significant risk to the life of patient than viral meningitis. So further investigations are required to differentiate them.

With these facts kept in mind the present study was carried out with the aim to evaluate the usefulness of CSF-CRP in differentiating bacterial from non-bacterial meningitis.

II. Materials And Methods

This hospital based prospective study was conducted in Department of Medicine in Gauwahati Medical College and hospital over one year.

All patients with fever, headache and signs of meningeal irritation with or without altered sensorium were put to CSF study. Those conforming to either bacterial or aseptic meningitis group (as described later on) were included in the analysis.

History and clinical findings of all the patients were recorded in a proforma.

In the first 24 hours of hospitalization, all cases underwent lumbar puncture and CSF samples were collected. CSF was then sent for CRP estimation, cytology, biochemistry, bacteriology, culture and sensitivity. CSF CRP was determined by simple antigen antibody precipitation test, *i.e.*, latex slide agglutination method with the help of commercially available kit. Presence of agglutination indicates CSF-CRP concentration of more than 6 µg/ml and was considered positive. Based on clinical, biochemical, cytological, microbiology and serological study of CSF the subjects were divided into two groups *i.e.*, pyogenic and aseptic meningitis.

'Bacterial meningitis group' were those whose CSF yielded polymorphonuclear leucocytosis, low glucose, moderate to highly elevated protein, positive gram stain and or culture. Lymphocytic pleocytosis with raised level of protein and significantly raised level of ADA were diagnosed to have Tuberculous meningitis and included in the same group.

The 'aseptic meningitis' group included those with negative CSF culture and gram stain, normal glucose, normal to slightly elevated protein, and absence of polymorphonuclear pleocytosis in CSF. Virus isolation as well as PCR could not be performed.

Statistical Analysis was done using statistics software IBM SPSS version 23. The tests used were Wilcoxon Rank sum Test, Mann-Whitney Test, Pearson Correlation and Chi-square test.

III. Results

During the study period a total of 50 patients were enrolled in this study after obtaining the informed written consent. The age of the patients in my study ranged from 13 years to 62 years. The mean \pm SD age of the patients was 29.8 ± 11.75 years with highest number of patients (30%) was observed in the age group of 21 to 30 years. There were 34 males and 16 females with a male:female ratio of 2.1:1.

According to serum & CSF analysis 28 cases had pyogenic meningitis 22 cases had aseptic meningitis. The mean values and ranges for CSF and serum markers in both groups are shown in table 1. The differences in the mean values were statistically significant for CSF protein levels, CSF leukocyte count, and CSF/serum glucose between bacterial and aseptic meningitis groups ($p < 0.001$). Values of serum CRP had significant difference in bacterial meningitis group compared to other group ($p < 0.001$).

Table 1:

Variables		Bacterial meningitis group (n=28)	Aseptic meningitis group (n=22)
Serum glucose (mg/dl)	Mean \pm St.deviation	119.28 \pm 32.98	115.09 \pm 20.31
	Range	76-220	80-170
CSF glucose (mg/dl)	Mean \pm St. deviation	42.39 \pm 9.89	50.54 \pm 8.46
	Range	26-70	40-78
CSF glucose/serum glucose	Mean \pm St.deviation	0.36 \pm 0.05	0.44 \pm 0.06
	Range	0.26-0.55	0.36-0.61
WBC count of CSF/ μ l	Mean \pm St.deviation	551.46 \pm 228.82	45.68 \pm 16.99
	Range	250-1200	10-90
CSF protein (mg/dl)	Mean \pm St. deviation	126.03 \pm 29.43	57.95 \pm 16.09
	Range	80-212	36-110
Serum CRP (mg/L)	Mean \pm St. deviation	91.29 \pm 46.1	19.72 \pm 14.47
	Range	34-190	5-70

In the bacterial meningitis group a total of 11 (39.29%) gram smear results were positive in contrast to other group in which no positive result were recorded. Organisms isolated are tabulated in Table 2.

Table 2: Organisms isolated in the bacterial meningitis group

Organism isolated	No. of cases
Pneumococcus	3
Meningococci	1
Klebsiella	1
Pseudomonas	1

Serum CRP levels were elevated in 27 patients. Of these 23 patients were in bacterial meningitis group in contrast to 4 patients in aseptic meningitis group . This correlation was found to be statistically significant as shown in Fig. 1.

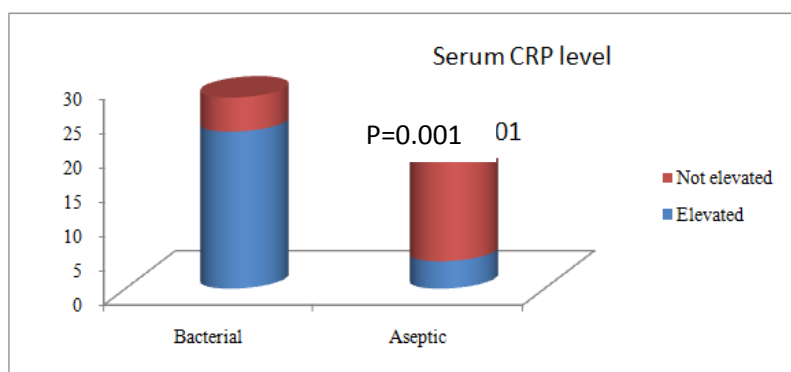


Figure 1: The Bar diagram showing serum CRP levels in bacterial & aseptic meningitis group

CSF CRP was positive in 23 cases. Out of these 21 cases were in bacterial meningitis group and 2 cases were in aseptic meningitis group . This correlation was found to be statistically significant (p=0.0007) .

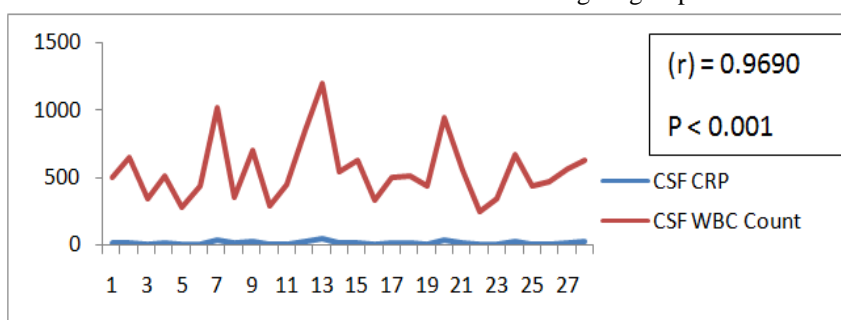
The Sensitivity, specificity, positive predictive value and negative predictive value of CSF-CRP and other variables for diagnosis for bacterial meningitis are shown in Table 3 .

Table 3

Variable	Accepted criteria for diagnosis of meningitis	Sensitivity	Specificity	Positive predictive value	Negative predictive value
CSF Glucose	< 40 mg/dl	61%	86%	79%	53%
CSF Glucose/serum glucose	< 0.4	92%	82%	86%	82%
CSF Protein	>100 mg/dl	85%	82%	85%	82%
Neutrophil count of CSF	>60 %	78%	86%	88%	76%
Gram smear	Positive	39%	100%	100%	56%
Culture	Positive	21%	100%	100%	50%
Serum CRP	>40 mg/dl	82%	84%	87%	78%
CSF CRP	Positive	75%	91%	92%	75%

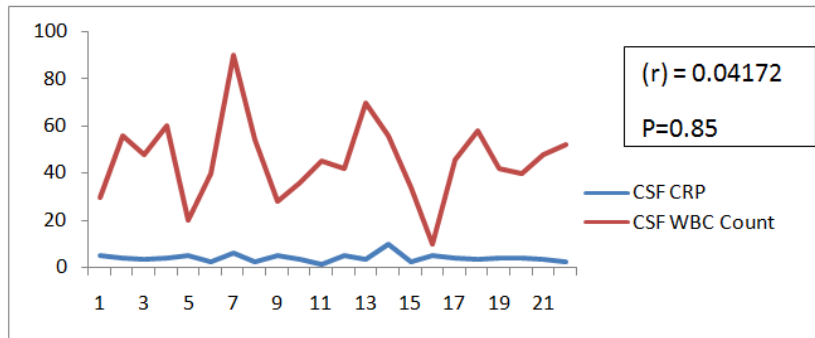
A significant correlation was found between CSF CRP and CSF glucose, CSF CRP and CSF protein, CSF CRP and Neutrophil count of CSF, CSF CRP and CSF glucose/serum glucose ratio.

Correlation between CSF CRP & CSF WBC count in Bacterial meningitis group



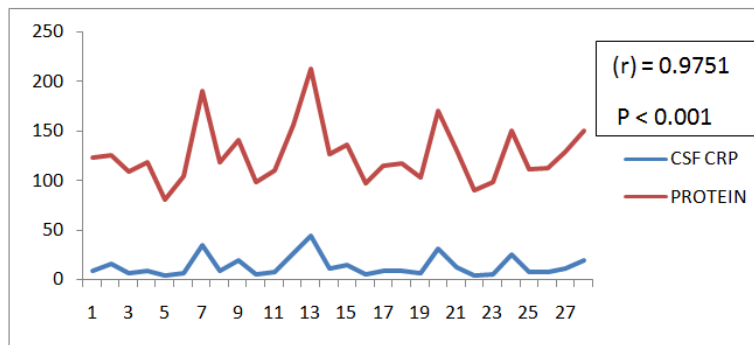
A significant positive correlation was found between CSF CRP & CSF WBC count in bacterial meningitis group.

Correlation between CSF CRP & WBC count in non-bacterial meningitis group



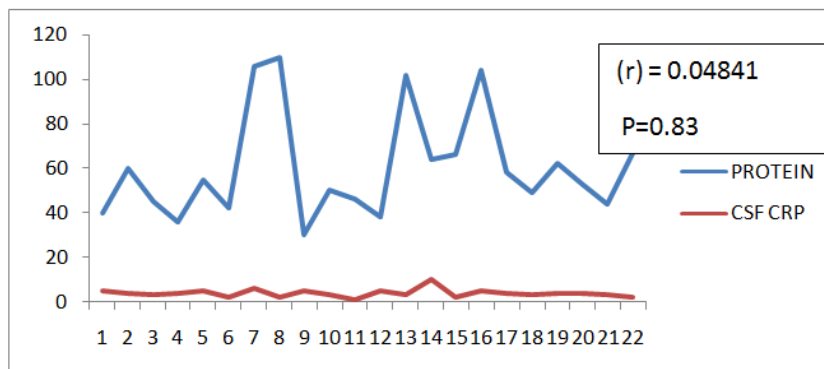
Correlation between CSF CRP & CSF WBC count in non-bacterial meningitis group was also positive but this relation was not statistically significant.

Correlation between CSF CRP & Protein in Bacterial meningitis group



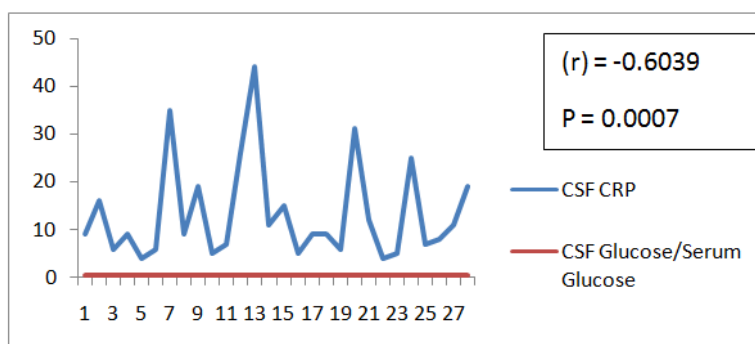
CSF CRP & CSF protein shared a significant positive correlation in patients with bacterial meningitis

Correlation between CSF CRP & Protein in Non-bacterial meningitis group



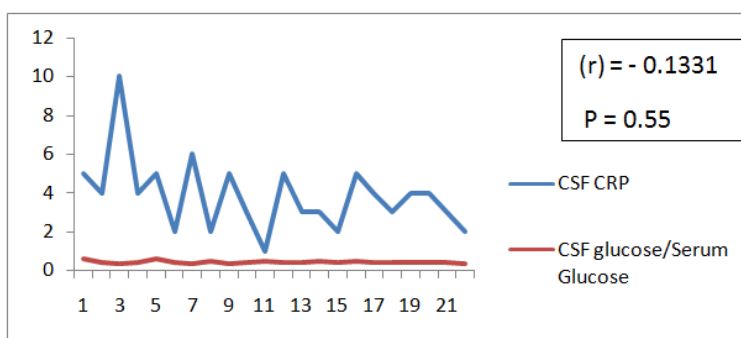
Correlation between CSF CRP & CSF protein in non-bacterial meningitis group was insignificant.

Correlation between CSF CRP & CSF Glucose/Serum Glucose ratio in Bacterial meningitis group



CSF CRP & CSF glucose/serum glucose ratio in bacterial meningitis group had a negative correlation which was statistically significant.

Correlation between CSF CRP & CSF Glucose/Serum Glucose ratio in Non-bacterial meningitis group



Correlation between CSF CRP & CSF glucose/serum glucose ratio in non-bacterial meningitis group was also negative but this relation was not statistically significant.

IV. Discussion

In our study, 50 cases were undertaken as per selection criteria. All the patients were subjected to detailed history taking, clinical examination and necessary investigations including imaging studies and laboratory tests. Consent was obtained from each patient (or their first-degree relative in case of altered sensorium) after fullexplanation of the nature and protocol of the study. Collected data were analyzed using suitable statistical methods as mentioned.

The mean \pm standard deviation (SD) age of all the subjects was 29.8 ± 11.75 years. The mean \pm SD age of the patients in bacterial meningitis group was 27.6 ± 14.22 years. The mean \pm SD age of the patients in non-bacterial meningitis group was 32.13 ± 6.28 years. This was statistically insignificant. ($p=0.17$). Jadali F et al, 2007^[8] also showed the difference between the groups (27.6 vs. 32.13) was not significant. Among all total 50 patients 34 were male and 16 were female. In the bacterial meningitis group there were 19 males & 9 females. The aseptic meningitis group comprised 15 males and 7 females. The two groups were comparable. Our study correlates with studies of Sormunen p et al, 1999^[9].

The mean WBC count in pyogenic meningitis group was 551.46 ± 228.82 cells/ μ l. In contrast to 45.68 ± 16.99 cells/ μ l in the non-bacterial group. This correlation was statistically significant. ($p < 0.0001$). Vaidya A K et al, 1987^[10] also showed similar result. Mean WBC count difference in two groups was significant. (603.23 ± 250.78 vs. 52.33 ± 18.27).

Mean Neutrophil count in pyogenic meningitis group was 56.42 ± 25.88 %. In non-bacterial meningitis group it was 25.55 ± 11.19 %. The two-tailed P value is 0.0002, considered extremely significant. In our study, mean CSF glucose in pyogenic meningitis group was 42.39 ± 9.89 mg/dl, and in non-bacterial group it was 50.54 ± 8.46 mg/dl. ($p=0.003$). Jadali f et al, 2007^[8] also found an elevated level of mean glucose in non-bacterial meningitis group. (31.3 ± 17.5 vs. 65.8 ± 18.8).

Mean CSF glucose/serum glucose ratio in both groups were 0.36 ± 0.05 and 0.44 ± 0.06 respectively which was statistically significant. ($p < 0.001$). Similar result was found by other studies. (Tankhiwale S S et al 2001)^[11], (Jadali F et al 2007)^[8]

We found a significantly high level of protein in bacterial meningitis group (mean 126.03 ± 29.43 mg/dl) in contrast to non-bacterial meningitis group. (mean 57.95 ± 16.09 mg/ dl). ($p < 0.001$). In a similar study conducted by Tatar R et al, 2000^[12] similar result was reported. mean protein level in both groups were as follows: pyogenic meningitis group - 87.5 ± 51.9 , non-bacterial meningitis group - 39.4 ± 18.5 .

In our study gram smear was positive in 39% cases and positive culture was recorded in 21% cases of bacterial meningitis. In a similar study by Singh N et al, 1995^[13] CSF Gram staining was positive in 6 (24%) and CSF culture was positive in 4 cases (16%). On the contrary, (71%) positive cultures from CSF specimens in bacterial meningitis group were recorded by Sormunen P et al, 1999^[9]. A number of factors (e.g. specimen handling, prior antibiotic use) might explain the divergent results.

In our study CSF CRP was positive in 21 of 28 cases (75%) of bacterial meningitis group and in 2 of 22 cases (9%) of non-bacterial meningitis group. This correlation was statistically significant. ($P=0.0007$). Sensitivity, specificity, positive predictive value and negative predictive value of the test were 75%, 91%, 92% and 75% respectively. Similar results were reported by Singh U K et al, 1994^[14], Corral *et al*, 1981^[15]

However our study does not correlate with the following studies probably because of using a different method- laser nephelometry for detection of CSF CRP. CSF from patients with bacterial meningitis was tested for CRP by Phillip and Baker, 1983^[16], they found elevated CRP levels in only two of 11 patients with culture proved bacterial meningitis. In another study by Shaltout A et al, 1986^[17] Cerebrospinal fluid C-reactive protein was elevated in seven of 19 cases with culture-proven bacterial meningitis, in only one of 15 cases with viral meningitis, and three of 139 cases with no meningitis but the test was not sensitive enough for early differentiation between bacterial and viral meningitis.

A correlation analysis between CSF CRP & CSF WBC count reveals significant positive correlation in presence of bacterial meningitis. ($p < 0.001$). This correlation was also positive in aseptic meningitis group but it was not statistically significant. ($p=0.85$). Tankhiwale SS et al 2001^[11] also found similar result.

Though CSF Neutrophil count in both bacterial & non-bacterial meningitis group had a positive correlation with CSF CRP it was significant only in bacterial meningitis group. ($p = 0.03$). Sormunen P et al 1999^[9] reported similar result.

We found a negative correlation between CSF CRP & CSF glucose/serum glucose ratio in both bacterial & non-bacterial meningitis group but this was not statistically significant enough ($p = 0.55$) in non-bacterial meningitis group. Jadali F et al 2007^[8] also found a significant negative correlation ($p < 0.001$) between CSF CRP & CSF glucose/serum glucose ratio.

In our study CSF protein was significantly elevated in bacterial meningitis group. We found a significant & positive correlation ($p < 0.001$) between CSF CRP & CSF protein in bacterial meningitis group. Shaltout A et al 1986^[17] al also reported similar result. ($p < 0.05$).

Bacterial meningitis is a potentially devastating illness that requires prompt recognition and early appropriate therapy. There is certainly no value in performing the test if Gram stain or culture of the CSF demonstrate organism. But gram smear was positive in only 39% cases of bacterial meningitis. The problem was with the remaining 61% of cases. The value of CRP lies in the management of these Gram stain negative patients in whom delay, in the specific treatment will be devastating. CSF CRP was positive in 75% cases of bacterial meningitis with a specificity of 91% and positive predictive value of 92%.

V. Conclusion

The present study suggests that a patient with any degree of CSF pleocytosis and raised protein level who has a positive CRP in the CSF should be treated for presumed bacterial meningitis. Patients with low grade pleocytosis (less than 50 neutrophils/cm) who have normal CSF glucose and protein and a negative Gram stain and in whom the clinical picture is very suggestive of a viral etiology, the absence of CRP in the CSF may be an additional piece of information that will assist the clinician in withholding antibiotic therapy.

Our observations suggest that the routine use of CSF-CRP may be useful and patients with positive CRP in the CSF should be treated presumptively for bacterial meningitis. Thus, easily performed rapid CRP determinations can considerably improve the quality of care in meningitis patients, especially in those situations where facilities for performing bacterial cultures of antibiotic susceptibility testing are not available.

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