

## Original Research Article

# Study of CSF C-reactive protein in meningitis to differentiate bacterial meningitis from aseptic meningitis in children between 1 month and 12 years of age

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### ABSTRACT

**Background:** Meningitis is a serious illness of childhood. CSF Gram stain and culture is the gold standard for diagnosis which is costly and time consuming. So, this study was conducted with the objective to measure the specificity, sensitivity, positive and negative predictive values and diagnostic accuracy of CSF-CRP in the diagnosis of bacterial meningitis.

**Methods:** This prospective study was conducted in Department of Pediatrics National Institute of Medical Sciences and Research, Jaipur. Children between 1 month to 12 years of age admitted with acute history of fever and seizure were included. CSF was sent for CRP estimation and other laboratory investigations. CSF CRP was determined qualitatively and value >6mcg/ml was considered positive. Patients were divided into three groups based on clinical and CSF findings. Group 1 (Bacterial meningitis), Group 2 (Aseptic Meningitis) and Group 3 (No meningitis/Control Group). Statistical analysis was done using software SPSS version 23.

**Results:** 120 patients were enrolled in our study. 65% of our cases were males. The mean age of our cases was 74.9±39.8 months. 48 cases had bacterial meningitis, 42 cases had Aseptic Meningitis and 30 cases had no meningitis. CSF-CRP was positive in 35 cases of Bacterial meningitis, 6 cases of aseptic meningitis and negative in all cases of control group. Hence the Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value and Diagnostic Accuracy of CSF-CRP for diagnosis of bacterial meningitis were 72.92%, 85.71%, 85.71%, 73.47% and 78.89% respectively. CSF-CRP cases of bacterial meningitis were also found to have a poor outcome.

**Conclusions:** CSF-CRP can be used as an initial test for the diagnosis of Bacterial Meningitis till other confirmatory test reports are awaited.

**Keywords:** Cerebrospinal fluid, C-reactive protein, Meningitis

### INTRODUCTION

Meningitis is a common serious illness during infancy and childhood and is an important cause of morbidity and mortality children.<sup>1</sup> Case fatality ranges from 5-50% depending upon the level of care provided with higher rates in developing countries like India.<sup>2-4</sup> A further 15-20% of survivors sustain neurological sequelae.<sup>5,6</sup>

Cerebrospinal Fluid (CSF) Gram stain and culture is the gold standard for diagnosis of pyogenic meningitis. However only 30-60% of pyogenic meningitis cases are culture positive.<sup>7</sup> Moreover the procedure requires skill, is costly and time consuming (preliminary results are delayed for at least 48 hours). Non-specific indicators like CSF glucose and protein level and CSF leukocyte and neutrophil counts are most of the times employed to diagnose etiology of meningitis. However, administration

of inadequate and inappropriate antibiotics prior to diagnostic test may cause alterations in the biochemistry and cytology of CSF and organisms may not be isolated from CSF thereby misleading the diagnosis.<sup>8</sup> Hence patients with aseptic meningitis receive antibiotics for extended duration causing economic burden and lengthening of hospital stay.

C-Reactive protein (CRP) is an acute phase reactant. Almost any inflammation in the body causes CRP to be detected in serum or other body fluids associated with the affected tissues.<sup>9,10</sup> In Western countries, attention has been directed to the value of serum CRP values to differentiate bacterial and viral infections.<sup>11</sup> Few studies have reported CSF C-reactive protein to have high sensitivity and specificity in differentiating pyogenic meningitis from aseptic meningitis.<sup>9,12,13</sup>

India is a developing country, with limited resources and skilled manpower particularly in peripheral set up. Hence there is a need for an easy and comprehensive test to diagnose Acute Bacterial Meningitis timely. Routine use of CSF CRP in diagnosing acute bacterial meningitis could be a rapid, reliable and easy method for diagnosis of meningitis.

So, this study was conducted with the objective to measure the specificity, sensitivity, positive and negative predictive values and diagnostic accuracy of CSF-CRP in the diagnosis of bacterial meningitis.

## METHODS

This hospital based prospective case controlled study was conducted in Department of Pediatrics National Institute of Medical Sciences and Research, Jaipur from 1<sup>st</sup> June 2015 to 31<sup>st</sup> May 2016.

All children between 1 month to 12 years of age admitted with acute history of fever and seizure were included in the study after taking a written informed consent. Children who received antibiotic for more than 24 hours before CSF study or had congenital central nervous system abnormality or suffering from any chronic illness were excluded from this study.

History and clinical findings of all the patients were recorded in a proforma. CSF samples were collected by performing a lumbar puncture by all aseptic techniques before starting any antibiotics. CSF was then sent for CRP estimation, cytology, biochemistry, bacteriology, culture and sensitivity. Blood sample were also sent simultaneously to estimate random sugar and blood counts.

CSF CRP was determined qualitatively by rapid slide latex agglutination method using diagnostic kits supplied by Span Diagnostics Limited. C-Reactive protein (CRP) >6mcg/ml was considered as a positive test. CSF culture was done by conventional methods.

Patients were divided into three groups based on clinical and CSF findings.<sup>14</sup> Group 1 (Bacterial meningitis) was defined by a CSF leukocyte count of 100–10,000/mm<sup>3</sup> with polymorphonuclear neutrophils (PMNs) of >50%, a CSF glucose level <2/3 blood sugar level, and a CSF protein level of 100-500 mg/dl with bacteria isolated from CSF culture. Group 2 (Aseptic Meningitis) was defined as those with a CSF pleocytosis of <100/mm<sup>3</sup> with lymphocyte predominance, protein levels of 50-200 mg/dl, and normal glucose levels with a negative bacterial culture and Gram stain. Group 3 (No meningitis/Control Group) included patients with fever and convulsions but normal CSF study. These convulsions were caused by epilepsy or febrile convulsions.

All patients were treated adequately (if culture positive according to sensitivity) and were monitored as long as they stayed in hospital. Outcome was assessed clinically during discharge.

Statistical analysis was done using statistics software IBM SPSS version 23. For significance of test Pearson chi square test was done Statistical significance was considered when P value was less than 0.05.

## RESULTS

During the study period 120 patients were enrolled in our study after written informed consent was obtained. 65% of our cases were males. The mean age of our cases was 74.9±39.8 months (Range 3-144 months).

Depending on the CSF cytology, biochemistry and bacteriology 48 cases had bacterial meningitis and were included in Group 1, 42 cases had Aseptic Meningitis and were included in Group 2 and 30 cases had no meningitis hence included in Group 3. Laboratory characteristics of the cases are tabulated in Table 1.

**Table 1: Laboratory characteristics of the cases.**

Parameters	Group 1 n=48	Group 2 n=42	Group 3 n=30
Total WBC (mm <sup>3</sup> ) Range (Mean)	110 - 18,000 (7064)	40 - 468 (236)	0-4 (2)
PMN (%) range (mean)	60 - 88(74)	0 - 45 (19)	0 (0)
Protein (mg/dl) range (mean)	108-580 (280)	52 - 190 (106)	15 - 38 (22)
Glucose (mg/dl) Range (mean)	(11-70) (24)	36 - 75 (58)	54 - 76 (66)
CSF-CRP (positive)	35(72.9%)	6(14.3%)	0

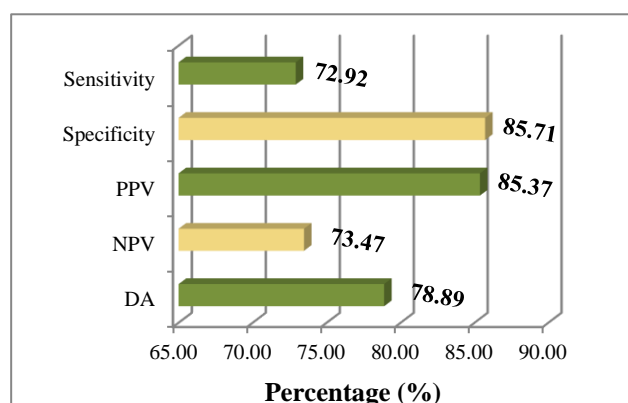
Organisms isolated in the bacterial meningitis group is tabulated in Table 2.

**Table 2: Organisms isolated in the bacterial meningitis group.**

Organism	N	%
<i>S. pneumonia</i>	20	41.67
<i>H. influenza</i>	17	35.42
<i>N. meningitides</i>	9	18.75
<i>E. coli</i>	2	4.16
Total	48	100

CSF-CRP was positive in 35 (72.9%) cases of Bacterial meningitis, 6 (14.3%) cases of aseptic meningitis and negative in all cases of control group.

Hence the Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Diagnostic Accuracy (DA) of CSF-CRP for diagnosis of bacterial meningitis are as shown in Figure 1.



**Figure 1: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (DA) of CSF-CRP.**

The outcome of bacterial meningitis cases is tabulated in Table 3. Cured was defined as improvement with no obvious sequel whereas not cured was defined as death or obvious sequel at end of treatment.

**Table 3: Outcome in the bacterial meningitis group.**

Outcome	CRP Result	
	Positive	Negative
Cured	12	10
Not-Cured	23	3
Total	35	13

On analysing the outcome of CSF-CRP cases in the bacterial meningitis group it was observed that cases with CSF-CRP positive had a statistically significant worse outcome as compared to CSF-CRP negative cases (Chi-square = 6.941 with 1 degree of freedom; P = 0.008).

**DISCUSSION**

Bacterial meningitis is a life-threatening illness. Early recognition and appropriate antibiotic treatment is crucial

to reduce morbidity and mortality. In developing country like India facilities to appropriately isolate blood- or CSF-borne organisms is scarce and if available culture reports are time consuming. There is a requirement of a test which is easy, quick, cheap and reliable to diagnose the aetiology of meningitis at the bedside. CSF-CRP is a test which meets all this criterion and unlike CSF cytology and biochemistry does not require a lot of knowledge to interpret the results. Our results suggest that CSF CRP can be used in situations where isolation of organisms is difficult.

In our study, CSF-CRP was positive in 35 (72.9%) cases of Bacterial meningitis, 6 (14.3%) cases of aseptic meningitis and negative in all cases of control group. Singh N et al in their study had reported that 84% of their cases of pyogenic meningitis had a positive CSF-CRP.<sup>13</sup> John M et al also in their study reported that 91% of the case of bacterial meningitis were CSF-CRP positive.<sup>15</sup> Malla KK et al in their study have also reported a statistically significant higher level of CRP in CSF of patient with bacterial meningitis as compare to those with aseptic meningitis.<sup>16</sup> However, Khanam R had reported only 35% of bacterial meningitis cases to be CSF-CRP positive.<sup>17</sup>

Our study reported the CSF-CRP to have a Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Diagnostic Accuracy (DA) of 72.92%, 85.71%, 85.71%, 73.47% and 78.89% respectively. Singh N et al in their study concluded that CSF-CRP had a sensitivity of 84%, specificity of 100% and a positive predictive value of 100%.<sup>13</sup> Pemde HK et al in their study reported that CSF CRP test showed 100% sensitivity and negative predictive values, 95-100% specificity and 94-100% positive predictive values.<sup>18</sup> Khanam R et al in their study reported Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) to be 35%, 100%, 100% and 53.6% respectively.<sup>17</sup>

CRP migration to CSF is not properly explained in literature. CSF-CRP levels were found to be lower than that of serum CRP. This difference was explained by direct hepatic release of CRP into plasma which then undergoes ultrafiltration to form CSF.<sup>19</sup> Diffusion of serum albumin and globulin across the inflamed meninges has been demonstrated and it seems feasible that CRP may cross from serum to CSF in a similar fashion. Passive diffusion across the highly-inflamed meninges would be a reasonable explanation as to how CRP gains access to CSF.<sup>20</sup> Our study also reported that a positive CSF-CRP is a poor prognostic indicator in bacterial meningitis. Similar observations were also reported by Khanam R et al.<sup>17</sup>

This study was limited by a small sample size and lack of quantitative estimation of CSF-CRP. A larger sample size and quantitative estimation of CSF-CRP would have given a better insight. This study was also limited as

other causes of meningitis like tubercular and fungal were not considered.

## CONCLUSION

This study concludes that CSF-CRP has a high sensitivity, specificity, NNV, PPV and diagnostic accuracy and can be used as an initial test for the diagnosis of Bacterial Meningitis till other confirmatory test reports are awaited.

This study also suggests that positive CSF-CRP in patients of bacterial meningitis indicated a poor prognosis.

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