



## Original article

# C-reactive protein in cerebrospinal fluid and serum: A paraphernalia in the diagnosis of pyogenic meningitis

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### Abstract

Meningitis is one of the commonest and most feared neurological diseases in children and adults with high morbidity and mortality. Analysis of cerebrospinal fluid (CSF) in meningitis by routine tests does not always provide rapid definite information as far as causative agent is concerned and there is need for additional tests on CSF. Estimation of CSF C-reactive protein (CRP) and comparing it with the levels of serum CRP levels can overcome this difficulty. In view of this background, the present study was undertaken to evaluate the sensitivity of CRP in CSF and its relation to the serum values. 32 cases of pyogenic meningitis between 18 to 65 years and 28 individuals undergoing lumbar puncture for various surgical procedures were taken as controls from Neurology department of Government General Hospital, Vijayawada. Lumbar puncture was done in all cases and CSF was collected in sterile bottles and blood was drawn within 1 hour of lumbar puncture. Analysis of the samples was done in the Departments of Biochemistry, Microbiology and Pathology of Siddhartha Medical College, Vijayawada. CRP was estimated using Latex Slide Agglutination semi quantitative method (Accurex). ANOVA, Chi-Square test and Z test were used for statistical analysis. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) was defined for each test. Receiver operating characteristic (ROC) curves were plotted. CSF protein was significantly high and CSF/serum ratio was altered. In majority of cases CSF sugar was less than 2/3 of blood sugar and absent in many of them. CRP was positive in almost all cases and was in the range of 0.6 to 9.6 mg/dl and values were corresponding in the serum. CSF CRP is a novel marker with high sensitivity and specificity. CRP can be used as a supportive evidence of meningitis, as these tests are cost-effective and it can be used on regular basis along with other routine tests to diagnose pyogenic meningitis in adults.

**Key words:** CRP, CSF, meningitis

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Acute infections of the nervous system are among the most important diseases in medicine because early recognition, efficient decision making, and rapid institution of therapy can be life saving. These distinct clinical syndromes include acute bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess, subdural empyema and infectious thrombophlebitis. Each may present with a non-specific prodrome of fever and headache followed by altered sensorium, focal neurological signs and seizures may appear. Many organisms can cause infections of the central nervous system (CNS). Bacteria are the most important cause of fever associated with signs and symptoms of CNS disease.

Meningitis implies primary involvement of meninges<sup>1</sup>. Nonetheless, specific pathogens are identifiable and are influenced by the age and immune status of the host and epidemiology of the pathogen<sup>2</sup>. Many acute phase markers are known to be present in abundance in the nervous system. Meningitis disturbs the blood brain barrier (BBB) and is expected to cause rise in their activity. Therefore, various investigators have used them for the diagnosis as well as for determining the prognosis in cases of meningitis. However the role of various cerebrospinal fluid (CSF) markers needs to be evaluated as not enough work has been carried out and majority of workers have estimated one of these acute phase reactants either in CSF or serum<sup>3</sup>. It is in this context that the present study was planned to evaluate the diagnostic significance of cerebrospinal fluid CRP in cases of pyogenic meningitis.

## Materials and methods

### Study design

A prospective clinical study with suspected/clinically diagnosed cases of pyogenic meningitis and appropriate controls was undertaken for CSF analysis with special reference to protein, glucose and CRP estimation.

### Subjects

The current study was conducted among adults between the ages of 18 and 65 years admitted in the General Medicine and Neurology wards of Government General Hospital, Vijayawada from May 2010 to August 2015.

Those cases admitted with fever, headache, vomiting, altered sensorium, with or without convulsions in the age group of 18 – 65 years were examined in detail for any clinical evidence of meningitis. Clinically evident cases of meningitis were random-

ly selected and submitted for detailed history and careful physical examination. In the clinical evaluation special attention was given for detection of any other associated pyogenic infection like pneumonia, sinusitis, otitis media, etc.

The study included the clinical evaluation and CSF analysis of 32 cases of meningitis and 28 other patients were taken as controls on whom lumbar puncture was performed for various surgical procedures. Patient attendee's were apprised of the purpose of study and written consent was taken prior to commencement of the study. Ethical clearance was obtained by the ethical clearance committee of the institution.

### Study protocol

In stable cases, after detailed clinical and fundal examination, lumbar puncture was performed immediately whereas in sick cases and cases with evidence of raised intracranial tension lumbar puncture was postponed till the patient stabilized. Blood was drawn for estimation of blood sugar, proteins CRP within 1 hour of lumbar puncture. During lumbar puncture pressure was assessed and macroscopic appearance of fluid was noted. 5-6ml of CSF was collected in 3 clean sterile bottles. For culture and sensitivity CSF was directly collected into glucose broth and sent to microbiology laboratory. One drop of CSF was collected directly over three clean glass slides. One slide was used to study pleocytosis and type of cells. The other two slides were used for preparation of smear by heat fixation for grams stain and ZN stain. Those cases of dry or traumatic tap were excluded from the study. Serum sample was collected using sterile technique from the median cubital vein in two vials one plain and the other containing sodium fluoride.

### Analysis of CSF and serum

All the samples (serum and CSF) were immediately taken for biochemical analysis of sugar, proteins, CRP. CSF and serum glucose estimation was done by Glucose Oxidase Method<sup>4</sup>. CSF protein estimation was done by turbidimetric method using 3% sulphosalicylic acid<sup>5</sup>. Serum protein estimation was done using Biuret method<sup>6,7</sup>. CSF and serum CRP estimation was done by semi-quantitative latex agglutination test<sup>8,9</sup>. CSF cytology was studied in the department of Pathology. Two slides and CSF collected in media were taken to the department of Microbiology for identification of organism. In all the cases the smears were stained with gram and ZN stain for the identification of organism. The specimen collected in the glucose broth was sub

cultured in the appropriate media and incubated at 37°C for 24 hours. The organism were identified by growth, character, direct microscopy and using other cytochemical studies. In all cases one sample was kept for cob web formation. The diagnosis of meningitis was made on the basis of clinical evidence of meningeal irritation, CSF protein, glucose and pleocytosis.

#### Statistical analysis

Results were analyzed by Analysis of variance (ANOVA), Chi-Square test and Z test. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) was defined for each test. SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

#### Results

##### Age and gender distribution of patients studied and controls

Figure 1 shows the age distribution in the study and control groups. The majority (19) of patients were in the age group of 26-35 years. Among total 60 (cases and controls), 41 (68.33%) were males and 19 (31.66%) were females. Males were predominant in meningitis cases. Among 32 cases, 26 (81.25%) were males and 06 (18.75%) were females. Among 28 controls, males were 15 (53.57%) and females were 13(46.42%).

##### CSF and serum protein

CSF protein was increased in all the 32 cases (100%) of pyogenic meningitis. The mean CSF protein in cases was 368.875±494.808 mg/dl with Z value of 38.387 ( $p < 0.0001$ ) and was statistically significant when compared with controls. The mean CSF protein in controls was 47.357±26.630

mg/dl. The CSF protein showed sensitivity of 90.6%, specificity of 92.8%, positive predictive value of 93.5% and negative predictive value of 89.7% at cut off value of >88 mg/dl.

No significant difference was seen in serum proteins between cases and controls. The mean serum total proteins in cases was 5859.375±535.73 mg/dl and in controls was 5635.714± 693.47 mg/dl with Z value of 1.503 ( $p > 0.05$ ) which was statistically not significant.

##### CSF and serum glucose

CSF glucose was decreased in 24 cases (75%) and was normal in 8 cases (25%). The mean CSF glucose in cases was 33.656 ± 20.185 mg/dl with Z value of 7.599 ( $p < 0.0001$ ) and was statistically significant when compared with controls. The mean CSF glucose in controls was 70.642±17.51 mg/dl. The CSF glucose showed sensitivity of 71%, specificity of 100%, positive predictive value of 92.3% and negative predictive value of 92.8% at cut off value of ≤ 45mg/dl.

No significant difference was seen in serum glucose between cases and controls. The mean serum glucose in cases was 96.937±22.997 mg/dl and in controls was 104.892±22.521 mg/dl with Z value of 1.697 ( $p > 0.05$ ) which was statistically not significant.

A significant difference was seen in CSF/serum glucose ratio between cases and controls. The mean CSF/serum glucose ratio in cases was 0.348±0.196 mg/dl with Z value of 8.177 ( $p < 0.0001$ ) which was statistically significant when compared to controls. The mean CSF/serum glucose in controls was 0.678±0.110 mg/dl. CSF/serum glucose ratio was <0.6 in 29 cases (91%) and less than 0.4 in 25 cases (78%).

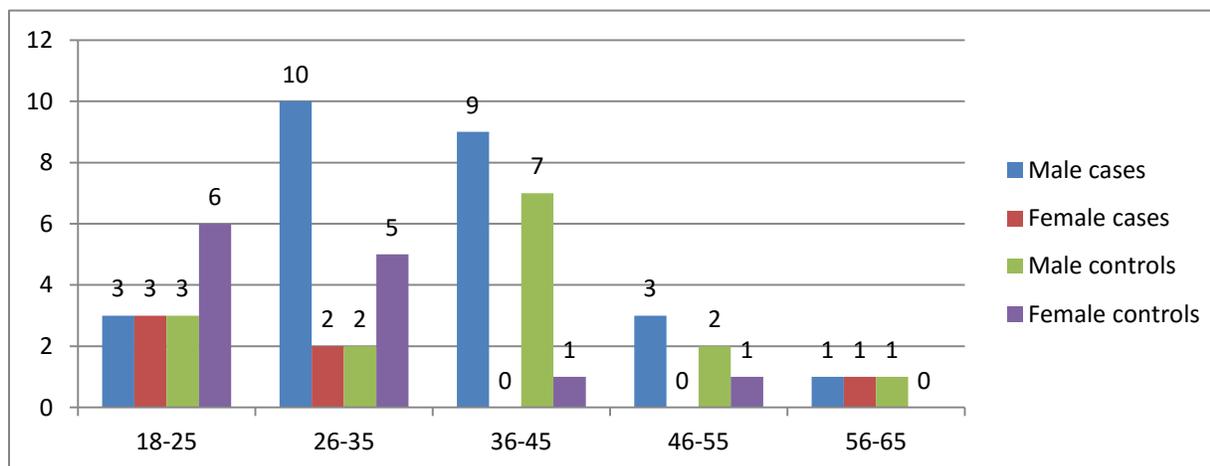


Fig 1. Age and gender distribution of cases and controls

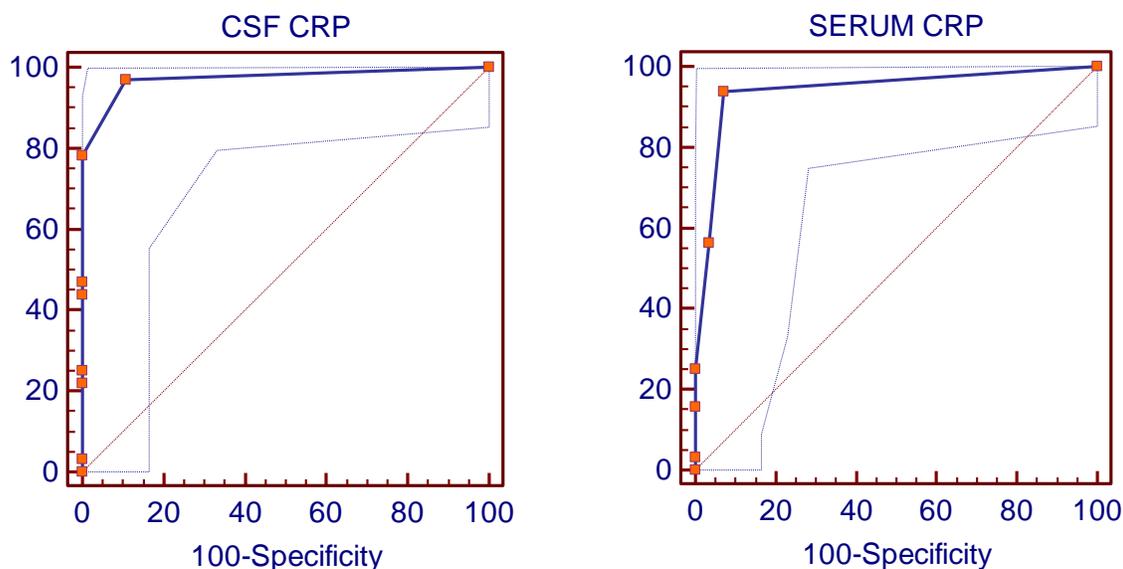
**CSF and serum C-Reactive Protein (CRP)**

CSF CRP was increased in 31 cases (96.8%) of pyogenic meningitis. The mean CSF CRP in cases was  $2.25 \pm 2.021$  mg/dl with Z value of 25.464 ( $p < 0.0001$ ) and was statistically significant when compared to controls. The mean CSF CRP in controls was  $0.064 \pm 0.188$  mg/dl. The CSF CRP showed sensitivity of 96.8%, specificity of 89.2%, positive predictive value of 91.1% and negative predictive value of 96.1% with cut off value  $> 0.6$  mg/dl.

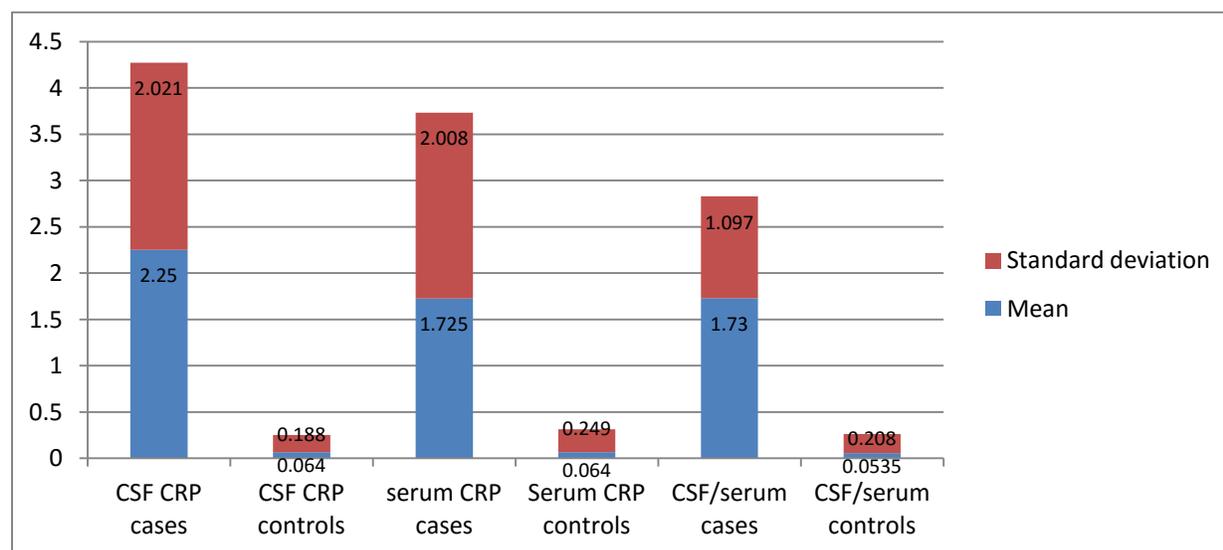
Serum CRP was increased in 30 cases (93.7%) of pyogenic meningitis. The mean serum CRP in cases was  $1.725 \pm 2.008$  mg/dl with Z value of 4.64 ( $p < 0.001$ ) and was statistically significant when

compared to controls. The mean serum CRP in controls was  $0.064 \pm 0.249$  mg/dl. The serum CRP showed sensitivity of 93.7%, specificity of 92.8%, positive predictive value of 93.7% and negative predictive value of 92.8%.

CSF/serum CRP ratio was increased in 30 cases (93.7%) of pyogenic meningitis. The mean CSF/serum CRP ratio in cases was  $1.73 \pm 1.097$  mg/dl with Z value of 8.5 ( $p < 0.001$ ) and was statistically significant when compared to controls. The mean CSF/serum CRP ratio in controls was  $0.0535 \pm 0.208$  mg/dl. The CSF/serum CRP ratio showed sensitivity of 93.7%, specificity of 92.8%, positive predictive value of 93.7% and negative predictive value of 92.8%.



**Fig 2.** ROC curves of CSF and serum CRP



**Fig 3.** CRP values in cases and controls

## Discussion

In this study of CSF analysis in pyogenic meningitis with special reference to proteins, glucose and CRP, 60 individuals were enrolled. Out of 60, 32 had pyogenic meningitis and 28 were controls who were posted for various surgeries.

There was a very significant elevation in levels of CSF protein in cases of pyogenic meningitis with a mean of  $368.875 \pm 494.808$  ( $p < 0.0001$ ) when compared to controls with a mean of  $47.357 \pm 26.630$ . The CSF protein showed sensitivity of 90.6%, specificity of 92.8%, PPV of 93.5% and NPV of 89.7%. Serum proteins showed no significant difference  $p > 0.05$ .

CSF glucose was very much decreased in 75% of cases with mean of  $33.656 \pm 20.185$  and was statistically significant ( $p < 0.0001$ ) compared to controls with mean of  $70.642 \pm 17.514$ . The CSF glucose showed sensitivity of 71%, specificity of 100%, PPV of 92.3% and NPV of 92.8%. There was no significant difference between the serum glucose levels of cases and controls. The CSF glucose in controls was about 67% of serum glucose whereas in cases it was 35%. CSF/serum glucose ratio corrects for hyperglycemia which can mask a decrease in CSF glucose concentration. The CSF glucose concentration is considered decreased when the CSF/serum ratio is less than 0.6. A ratio of  $< 0.4$  is highly suggestive of pyogenic meningitis<sup>10</sup>. In present study CSF/serum glucose ratio was  $< 0.6$  in 29 cases (91%) and less than 0.4 in 25 cases (78%).

CSF CRP was elevated in 97% of cases with mean of  $2.25 \pm 2.021$  and was statistically significant ( $p < 0.0001$ ) when compared to controls with mean of  $0.064 \pm 0.188$ . The CSF CRP showed sensitivity of 96.8%, specificity of 89.2%, PPV of 91.1% and NPV of 96.1%. Serum CRP was also increased in 94% of cases with mean of  $1.725 \pm 2.008$  and was statistically significant ( $p < 0.0001$ ) when compared to controls with mean of  $0.064 \pm 0.249$ . The serum CRP showed sensitivity of 93.7%, specificity of 92.8%, PPV of 93.7% and NPV of 92.8%. The CSF/serum CRP ratio was elevated in 94% of cases and was statistically significant ( $p < 0.001$ ).

### *CSF analysis comparison with other studies*

In the present study CSF protein value showed a highly significant increase with a mean of  $368.875 \pm 494.808$  mg/dl ( $p < 0.0001$ ) compared to the controls with mean of  $47.357 \pm 26.630$ . The CSF protein showed sensitivity of 90.6%, specificity of 92.8%, positive predictive value of 93.5% and negative predictive value of 89.7%.

Earlier studies showed similar trend with CSF protein, having mean of  $163 \pm 134.2$  mg/dl in the study by Jain et al<sup>11</sup> and  $469.6 \pm 251.5$  mg/dl in study done by Sharma et al<sup>12</sup>. Jadali et al<sup>13</sup> in their study observed an increased CSF protein with mean  $295 \pm 204.4$  mg/dl and a sensitivity of 73%, specificity of 93%, PPV of 90% and NPV of 80%.

The CSF glucose levels in cases showed a significant decrease with mean of  $36.781 \pm 28.162$  ( $p < 0.001$ ) when compared to CSF glucose levels in controls with mean  $70.64 \pm 17.51$ . The CSF glucose showed sensitivity of 71%, specificity of 100%, positive predictive value of 92.3% and negative predictive value of 92.8%. Our results correspond with previous works.

The CSF glucose of cases with mean of  $21.3 \pm 17.5$  when compared to CSF glucose of controls with mean of  $72.3 \pm 11.8$  was observed in the study done by Jadali et al<sup>13</sup>. Abro et al<sup>14</sup> had similar observations in their study with mean CSF glucose of  $26.50 \pm 21.56$ . The mean CSF glucose was  $16.9 \pm 8.17$  mg/dl in the study done by Sharma et al<sup>12</sup>, and levels were 38.1 mg/dl as observed by Sathpathy et al<sup>15</sup>.

The CSF CRP was increased significantly in 31 cases (96.8%) with a mean of  $2.25 \pm 2.021$  ( $p < 0.001$ ) when compared to controls with mean of  $0.064 \pm 0.188$  and showed a sensitivity of 96%, specificity of 89.2%, positive predictive value of 91% and negative predictive value of 96%. Serum CRP was also increased in 94% of cases with mean of  $1.725 \pm 2.008$  and was statistically significant ( $p < 0.001$ ) when compared to controls with mean of  $0.064 \pm 0.249$  and showed a sensitivity of 93.7%, specificity of 92.8%, PPV of 93.7% and NPV of 92.8%.

Our findings are consistent with a sensitivity of 80%, 100% specificity and 100% positive predictive value in study conducted by Gaur et al<sup>16</sup>. Prasad et al<sup>17</sup> showed that CSF CRP was sensitive in 86.6 % cases and specific for 92 % cases and showed a positive predictive value of 94% and negative predictive value of 82% whereas serum CRP has a sensitivity of 76% and specificity of 68%. Diaz et al<sup>18</sup> showed a sensitivity of 81 % of CSF CRP. Shimetani et al<sup>19</sup> also showed a substantial increase in CSF and serum CRP levels in cases of meningitis. Kumar et al<sup>20</sup> observed a very significant increase ( $p < 0.0001$ ) in CSF CRP levels with mean of 28.88 mg/dl in cases of pyogenic meningitis. Vaishnavi et al<sup>21</sup> and Takhiwale et al<sup>22</sup> observed a similar trend with the levels of CSF CRP.

### ROC curves

In the ROC analysis the following cut off values corresponding to highest diagnostic accuracy (minimal false negative and false positive results) work as follows.

Cut off value of >88mg/dl for CSF protein,  $\leq$  45mg/dl for CSF glucose, >0.6 mg/dl for CSF CRP. According to these values the best areas under the curves (AUC) are 0.980 for CSF protein, 0.871 for CSF glucose, and 0.973 for CSF CRP.

According to cut off values from ROC analysis, CSF CRP appeared highly significant in pyogenic meningitis when compared to the normal controls ( $p < 0.0001$ ). Other CSF parameters i.e., CSF proteins, CSF glucose are also significant.

### Conclusion

In most of the meningitis cases, detailed history and clinical examination and analysis of cells was helpful in diagnosing meningitis, CSF analysis was helpful in majority of the patients for accurate diagnosis of meningitis.

The biochemical profile observed in the present study which helped in diagnosing pyogenic meningitis was: low CSF glucose with mean of  $33.65 \pm 20.18$  ( $p < 0.0001$ ) and glucose CSF/serum ratio  $< 0.6$  in 91% cases and increased CSF protein with mean  $368.875 \pm 494.808$  ( $p < 0.0001$ ). CSF CRP was increased with mean of  $2.25 \pm 2.021$  ( $p < 0.0001$ ), serum CRP was increased with mean of  $1.725 \pm 2.008$  ( $p < 0.0001$ ) and CSF/serum CRP ratio of  $1.737 \pm 1.09$  ( $p < 0.001$ ) was observed and may be a sensitive parameter along with them.

To conclude in majority of cases the CSF glucose was decreased and CSF proteins were elevated. A corresponding increase in CSF and serum CRP was seen and CSF CRP appeared to be the best marker amongst them.

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**Conflict of interest:** None

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