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# Evaluation of Cerebrospinal Fluid C-Reactive Protein for Differentiating Pyogenic Meningitis from non Pyogenic Meningitis

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## Introduction

Acute infections of the nervous system have always remained a major cause of death and disability for millions of people around the world, despite decades of dramatic progress in their treatment and prevention. Each infectious disease can cause a spectrum of illnesses, (particularly those with underlying medical conditions like diabetes, cardiopulmonary disorders etc) posing great challenge to Physician's diagnostic skills, thus making their early recognition and rapid institution of therapy, essential for lifesaving.[4]

Meningitis remains an important cause of CNS infection in developing country like India with high mortality and morbidity. Meningitis is an inflammation of the leptomeninges and underlying subarachnoid CSF. Most cases of meningitis are caused by microorganisms such as bacteria, viruses, fungi or parasites that spread into blood and CSF. In the above context, meningitis has been divided into two groups, namely – Pyogenic Meningitis (Bacterial Meningitis) and Non-Pyogenic Meningitis (Tuberculous, Viral, Fungal etc.).[15]

Acute pyogenic meningitis is the most common cause of suppurative infection in Central Nervous System. The prognosis of pyogenic meningitis is critically dependent on a rapid and causal implementation of immediate treatment. Rapid and accurate diagnosis coupled with early appropriate therapy is of utmost importance in reducing morbidity and mortality of the patients. However, clinical and biochemical parameters available are not reliable enough except when bacteria are found in CSF. Furthermore, some patients may not present with many of the classic symptoms or signs of bacterial meningitis.[3]

Culture & sensitivity, Gram stain, cytology and biochemistry of cerebrospinal fluid (CSF) sample are traditionally being done to diagnose and to differentiate pyogenic from non-pyogenic meningitis. Proper culture is affected by prior antibiotic therapy, delay in transportation, inoculation etc. It takes more than 24 hours to isolate the organism. Gram stain lacks specificity and has interpretative errors. Further, probability of visualization of bacteria on Gram stain is dependent upon the number of organisms present. Therefore, treatment of acute pyogenic meningitis most of the time remains presumptive. In such circumstances the detection of C-reactive protein in cerebrospinal fluid appears to provide a new dimension to the diagnosis of meningitis.[3]

It is not an alternative of CSF culture, cytology and biochemistry, but for initial quick assessment it can be considered as first line investigation for suspected meningitis to differentiate pyogenic meningitis from non pyogenic cases especially in

rural or remote areas where investigation facilities are limited. The test does not require much expertise to conduct and interpret the result.[4]

Large number of studies conducted worldwide suggests that CRP level in the CSF is higher in pyogenic meningitis as compared to non-pyogenic meningitis and hence aids in the differential diagnosis and management of meningitis. But, there are very few studies supporting the same in our country. Hence this study was designed to evaluate the same in our population.

## Aims & Objectives

The current study was undertaken among adult patients of meningitis who presented to casualty or outdoor department of Medicine at Katihar Medical College, Katihar during the period Dec.2011 – Aug.2013:

- To evaluate the clinical presentation and CSF analysis in meningitis patients with special reference to C-Reactive Protein estimation in cerebrospinal fluid.
- To determine sensitivity, specificity, Positive predictive value, Negative predictive value and accuracy of C-Reactive Protein estimation in CSF for early diagnosis of Pyogenic meningitis.
- To differentiate pyogenic meningitis from non-pyogenic meningitis on the basis of CSF-CRP positivity as an initial, rapid diagnostic screening test.

## Material & Methods

The present study was carried out in Department of Medicine at Katihar Medical College, Katihar during the period Dec.2011-Aug. 2013. Patients attendants were appraised of the purpose of study and consent was obtained. The study included clinical evaluation and CSF analysis (as per proforma attached), of 60 cases of meningitis and 20 cases as controls for which clinical diagnosis (Neurological) was other than Meningitis such as febrile convulsion, seizures, epilepsy, mental retardation etc.

Based on the clinical findings and CSF analysis the study was divided into **three groups**:

**Group 1 :** Pyogenic Meningitis

**Group 2 :** Non-Pyogenic Meningitis

**Group 3 :** Control

**Group Design for the study**

| Group 1 | Group 2 | Group 3 |
|---|---|---|
| ***Pyogenic Meningitis*** | ***Non-Pyogenic Meningitis***<br>*Group 2a* – Tubercular Meningitis<br>*Group 2b* – Viral Meningitis | ***Control*** |

**Case Distribution in the three study Groups**

| *Type of Meningitis* | *Number* | *Percentage* |
|---|---|---|
| ***Pyogenic Meningitis*** | 30 | 37.5% |
| ***Non-Pyogenic Meningitis*** | 30 | 37.5% |
| ***Control*** | 20 | 25% |
| ***Total*** | **80** | **100%** |

## Observation & Discussion

This study was carried out with the endeavour to look out for a rapid, reliable, cost effective screening test which can be performed in any standard pathology laboratory for differential diagnosis of meningitis. Several rapid diagnostic tests have been used recently to determine the etiology of meningitis; Cerebrospinal fluid – C-reactive protein being one of them.

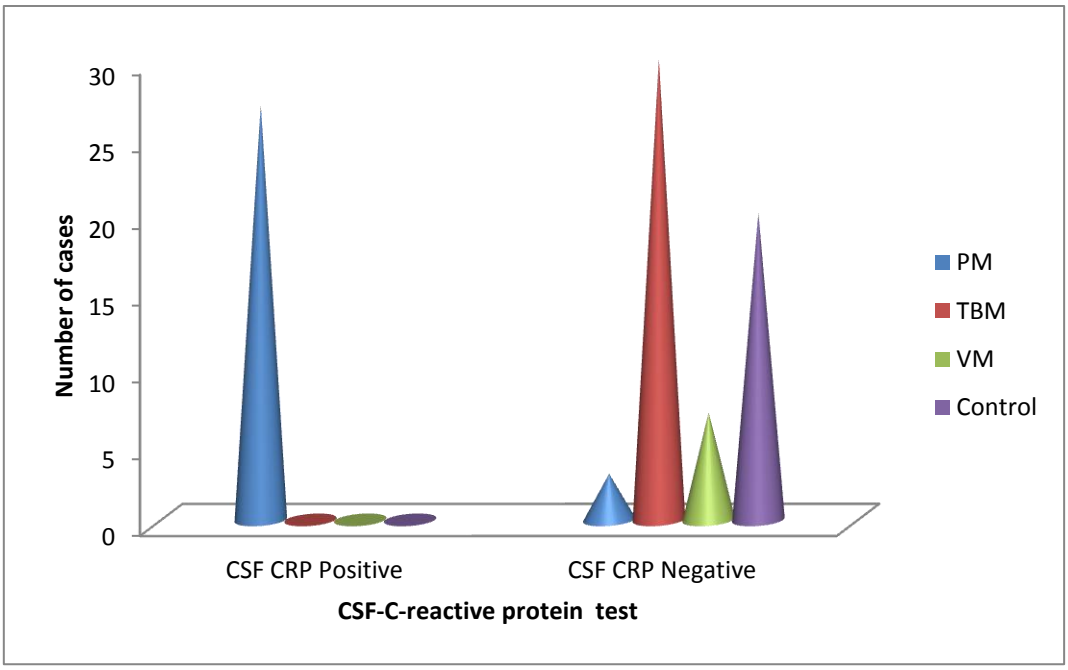
No doubt, the test has lived upto its expectations. Also it has been suggested that a Negative C-reactive protein test in Cerebrospinal fluid can be used with a very high probability to rule out pyogenic meningitis until proved otherwise.

The study included a total of 60 cases of meningitis and 20 cases of control. 30 cases were in the pyogenic group, 30 in non pyogenic group (23 cases of TBM & 07 cases of VM). The study was divided into three groups-Group1 included Pyogenic meningitis cases, Group 2 included Non Pyogenic meningitis comprising of mainly Tuberculous meningitis & Viral meningitis. Besides, there were 3 cases of Fungal meningitis but they could not be included in the study as they were immunocompromised and were on ART/Steroids (These factors are independently known to affect CSF-CRP levels). There was also a 3rd Group which included 20 cases of control in

which neurological clinical diagnosis was other than meningitis.

**1.CSF-CRP Test**

| GROUP | Diagnosis | Total No.of cases | CSF-CRP POSITIVE No. | % | CSF-CRP Negative No. | % |
|---|---|---|---|---|---|---|
| GROUP1 | PM | 30 | 27 | 90.0 | 03 | 10.0 |
| GROUP2 | NPM | 30 | 00 | – | 30 | 100 |
| GROUP3 | Control | 20 | 00 | – | 20 | 100 |




**CSF CRP Test (Positive/Negative)**

**2. Mean CSF-CRP Level in Different Study Groups**

| *GROUP* | *Type of Meningitis* | *Number* | *Mean CSF-CRP level (mg/l)* |
|---|---|---|---|
| ***Group 1*** | PYOGENIC MENINGITIS | 30 | 29.77 |
| | Gram negative organisms | 13 | 35.77 |
| | Gram positive organisms | 17 | 25.18 |
| ***Group 2*** | NON PYOGENIC MENINGITIS | 30 | 1.39 |
| | TBM | 23 | 1.50 |
| | VM | 07 | 1.03 |
| ***Group 3*** | CONTROL | 20 | 0.17 |

**3.(a) Diagnostic performance of CSF-CRP for differentiating pyogenic meningitis from non-pyogenic meningitis group**

| Test Result | Pyogenic Meningitis | Non-Pyogenic Meningitis | Total |
|---|---|---|---|
| **CSF-CRP Positive** | 27 | 00 | 27 |
| **CSF-CRP Negative** | 03 | 30 | 33 |
| **Total** | 30 | 30 | 60 |

(b)

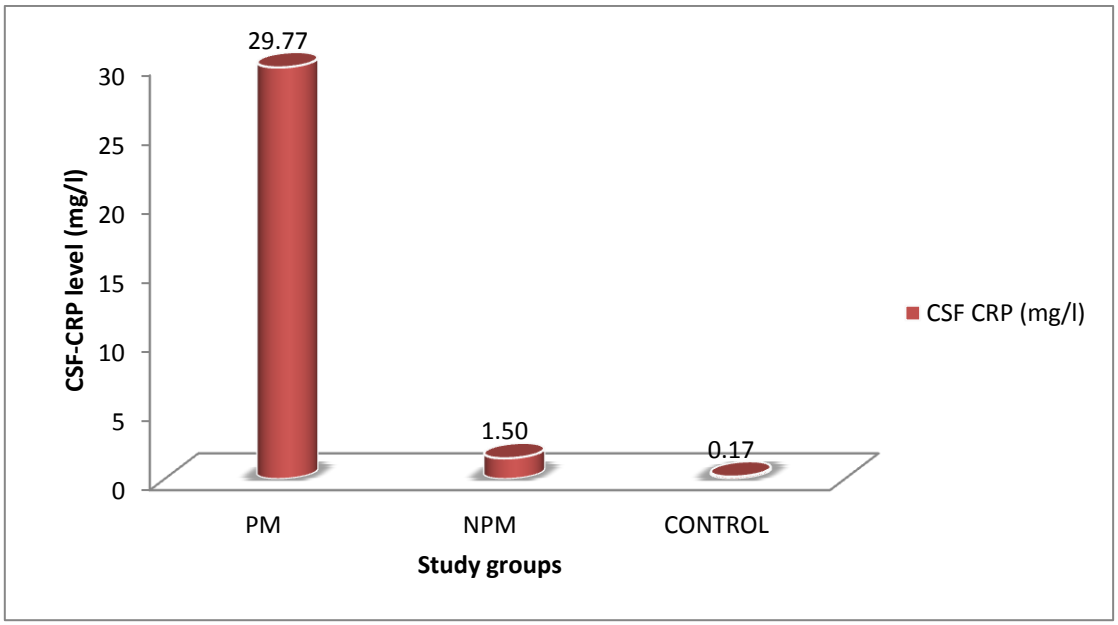
| | |
|---|---|
| ***Sensitivity*** | 90% |
| ***Specificity*** | 100% |
| ***Positive Predictive Value*** | 100% |
| ***Negative Predictive Value*** | 91% |
| ***Accuracy*** | 95% |
| ***P value*** | < 0.001 (** statistically significant) |

4(a) Diagnostic performance of CSF-CRP for differentiating pyogenic meningitis from control group

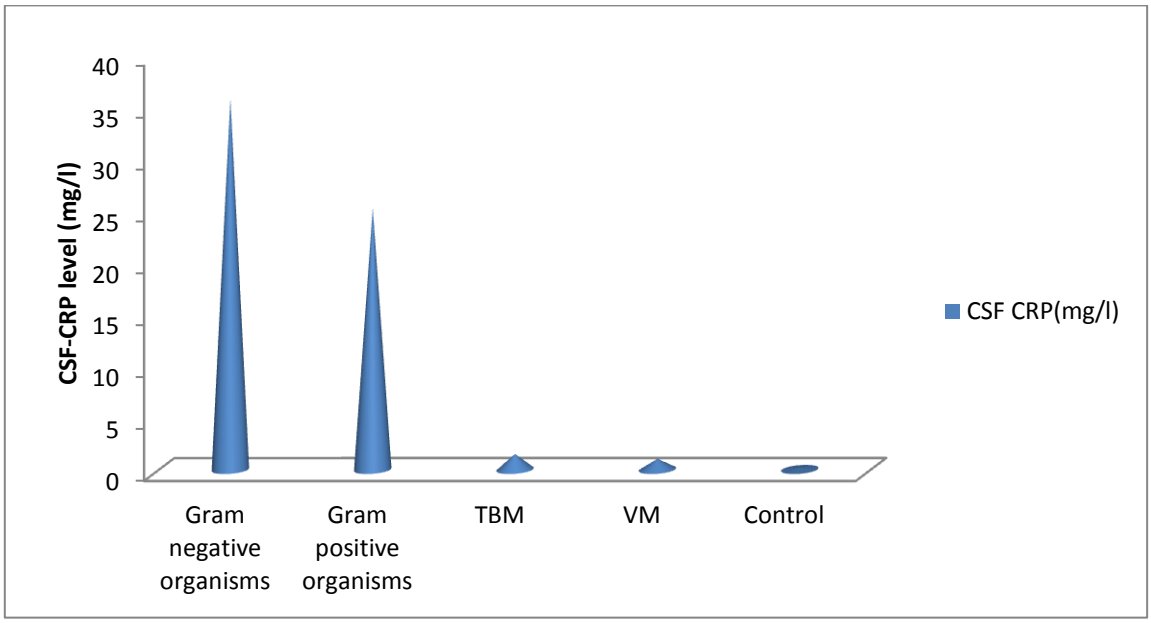
| Test Result | Pyogenic Meningitis | Control | Total |
|---|---|---|---|
| CSF-CRP Positive | 27 | 00 | 27 |
| CSF-CRP Negative | 03 | 20 | 23 |
| Total | 30 | 20 | 50 |

(b)

| | |
|---|---|
| ***Sensitivity*** | 90% |
| ***Specificity*** | 100% |
| ***Positive Predictive Value*** | 100% |
| ***Negative Predictive Value*** | 86.96& |
| ***Accuracy*** | 94% |
| ***P value*** | < 0.001 (** stastically significant) |




**Mean CSF-CRP values in different study groups.**




**Mean CSF-CRP level in different cases**

C-reactive protein in cerebrospinal fluid was determined by Immunoturbidimetric method. The CSF-CRP cut off value for this study was taken to be 6mg/l. CSF-CRP value >6mg/l were considered as positive test and values < 6mg/l were taken as negative. [Table15]

CRP levels are affected by factors such as hepatic dysfunction, dyslipidaemia, females on oral contraceptive pills, patients on steroids and hence were not included in the study[44].

Out of 30 cases of PM, CSF C-reactive protein was found to be positive (> 6mg/l) in 27 cases. There were Three cases of PM, out of which two were Gram positive and one Gram negative on Gram staining but CSF-CRP was negative (<6mg/l).

The CSF-CRP test was negative in all cases of TBM & VM (i.e CSF-CRP value was < 6mg/l).

There were 3 cases of Fungal meningitis i.e NPM where CSF-CRP values in 2 cases were 5 mg/l and in one case it ws4 mg/l. But unfortunately, these cases could not be included in the study as they were immunocompromised and were on ART/Steroid (These factors are known to independently affect CSF-CRP levels). However, fungal staining was positive and hence differentiating PM and TBM from fungal meningitis is not difficult[3]. Besides, by latex agglutination method CRP concentration below 6mg/l, agglutination does not occur on slide and this is considered as negative test.

In this study, the mean CSF-CRP level in pyogenic group was 29.77mg/l as compared to non-pyogenic meningitis = 1.39mg/l, which was statistically significant ($p < 0.001$).

Among the pyogenic group it was higher in those caused by Gram negative organisms (mean value=35.77mg/l) as compared to Gram positive organisms (mean value=25.18mg/l). The highest CSF-CRP value recorded by Gram negative organism was 46mg/l as compared to Gram positive organism, which was 34mg/l. This finding reflects the ability of endotoxin lipopolysaccharide-S, present in the Gram negative bacteria to affect the permeability of blood brain barrier or to induce local CRP production in CNS.

Among non pyogenic meningitis, it was slightly higher in tuberculous meningitis = 1.50mg/l as compared to viral meningitis = 1.03mg/l but this was not statistically significant.

In the control group the mean CSF-CRP level was found to be 0.17mg/l.

On comparing PM with NPM, the sensitivity and specificity of test was 90.0% and 100% respectively, with an accuracy of 95%. The Positive predictive value was 100% and NPV was 91% and p value was less than 0.001 which was statistically significant.

While comparing CSF-CRP values of PM with control group, the sensitivity and specificity was again 90% and 100% respectively with an accuracy of 94%. The PPV and NPV in this case was 100% and 86.96% respectively and p value was less than 0.001 which was again statistically significant.

On the basis of above results, it can be concluded that CSF-CRP levels were significantly higher in pyogenic meningitis compared to non pyogenic meningitis and control group which was stastistically significant ( $P < 0.001$ ). Hence, the test is quite useful for differentiating PM from NPM as well as control but it cannot differentiate between TBM & VM.

Observations of the present study is comparable to most of the studies done at different centres by different authors:

- Previous studies conducted by *Goran Rajs et al*, have observed that CSF-CRP levels are higher in Gram negative pyogenic meningitis compared to Gram positive pyogenic meningitis suggesting that infection with Gram negative bacteria probably enhances permeability of CRP through the blood brain barrier[7].

  A similar finding was seen in this study also. The CSF-CRP values ranged between 34-46mg/l in gram negative bacteria compared to 20-34mg/l in gram positive bacteria.

- A recent 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 pyogenic meningitis[23]. Similar finding was seen in this study also, with all TBM & VM cases turning out to be negative for CSF C-reactive protein test.
- In a study conducted by *Vaishnavi C et al* CRP in CSF was significantly higher in patients with pyogenic meningitis compared to tuberculous meningitis. Authors concluded that estimation of CSF-CRP can be used for preliminary differential diagnosis of meningitis[24].
  A similar finding was seen in this study also with CSF-CRP level being significantly higher in pyogenic meningitis compared to tuberculous meningitis or viral meningitis. The mean CSF-CRP level in PM was 29.77mg/l and in NPM it was 1.39 mg/l.
- *Riberio MH et al* estimated the levels of CRP in CSF from 33 patients with pyogenic meningitis, 21 patients with lymphocytic meningitis and 54 controls. No more than 4% patients, were incorrectly classified belonging to pyogenic group on the basis of measurement of CRP levels in CSF.[2]
  Similarly, in this study also there were only 3 cases out of 30 pyogenic cases which were CSF-CRP negative.
- *Hemvani V et al* evaluated the role of CSF-CRP in diagnosis of meningitis. The study included 499 CSF samples from cases of pyogenic, tubercular, viral and fungal meningitis and 580 normal CSF samples. The test was positive in 73.3% of samples from partially treated pyogenic meningitis and 92% among pyogenic meningitis cases. All suspected cases of TBM and VM were negative for the test. CSF-CRP was raised in 27.2% and 12.5% of CSF samples from candidial and cryptococcal meningitis cases. The study concluded that CSF-CRP estimation can be of great value to differentiate pyogenic meningitis from non pyogenic meningitis. However, it could not differentiate between tuberculous, fungal and viral meningitis[8].
  Similarly, in this study also the test was positive in 90% pyogenic cases making PM easier to distinguish from NPM but unable to differentiate TBM from VM.
- *Tankhiwale SS et al* investigated 75 clinically, biochemically and microscopically diagnosed cases of pyogenic meningitis including 28 adults and 47 paediatric patients. 31 out of 75 cases (42.66%) were positive for CSF-CRP while 34 were positive for serum CRP. Thus a total of 66 patients showed raised CRP IN CSF or serum. The result was statistically significant and hence, the authors concluded that CRP in CSF and serum can be used as an early marker for rapid diagnosis of pyogenic meningitis[10].
  Similarly in this study also raised CSF-CRP level was seen in cases of PM as compared to NPM.
- As per study done by *Pemde HK et al*, CRP in CSF is specific for pyogenic meningitis which is not detectable in aseptic meningitis, a fact also observed in this study. In viral meningitis, the tissue response is chiefly due to T cells, macrophage and necrotic tissues of caseous nature. These might be responsible for the binding of larger quantities of CRP molecules thereby permitting only a few of them to appear in CSF. This can be a probable explanation of undetectable level of CRP in CSF of viral meningitis/ tubercular meningitis. On the other hand, in pyogenic meningitis the chief cells are polymorphs lacking the site for binding of CRP molecules in the inflamed tissues allowing more CRP to accumulate in CSF which could be detected by CRP test[29].
- A study conducted at Seth GS Medical College of KEM Hospital, Mumbai, concluded that 100 culture proven bacterial meningitis cases and 26 cases of Tubercular meningitis had Cerebrospinal fluid – C-

reactive protein positive and 4 cases which were taken as viral meningitis, Cerebrospinal fluid – C-reactive protein was negative. This study suggested that Cerebrospinal fluid – C-reactive protein values appeared to be more sensitive in differentiating pyogenic and non pyogenic meningitis.

Similarly, the result of this study also suggests that CSF C-reactive protein level can be used as a rapid diagnostic test to differentiate PM from NPM.

- A study conducted at A study conducted in The Department of Clinical Biochemistry and The Department of Microbiology, Hadassah Mount Scopus Hospital, Jerusalem, concluded that the mean C-reactive protein in Cerebrospinal fluid was 143 +/- 2.1 mg/L in gram negative bacterial meningitis as compared to a value of 4 +/- 0.9 mg/L in gram positive bacterial meningitis.[8]

  Similarly, in this study also among PM, CSF-CRP level was higher in those caused by Gram negative organisms as compared to Gram positive organisms.
- A study conducted at JLN, Ajmer, Rajasthan, concluded that Cerebrospinal fluid-C-reactive protein levels in pyogenic meningitis were very high (104 +/- 90.21 mg/L), but within normal range in TBM, viral meningitis and controls (< 6mg/L).[8]
- Studies conducted by Pradowski et al observed that CSF CRP levels were significantly lower in non pyogenic meningitis compared to pyogenic meningitis[27].

  Similar findings were also seen in this study.
- Similar studies conducted by Przylalkowski et al indicated that CRP levels in CSF were elevated significantly in pyogenic meningitis compared to non pyogenic meningitis; a fact which was also observed in the present study[4].

**Summary & Conclusion**

The etiological diagnosis of meningitis in developing countries remains a problem in clinical practice as CSF biochemical analysis and cellular responses often overlap. This becomes even more difficult in a population where TBM is prevalent, as Mycobacterium tuberculosis is not always easily and reliably identifiable in CSF by established methods. The result of this study indicates that demonstration of CSF-CRP in initial stage is an ideal method in such situations.

Early, confirmatory diagnosis and aggressive management can help prevent serious CNS complications and at the same time reduce unwarranted or harmful therapy for patients. In this regard, a number of studies have been conducted worldwide recently, which strongly suggests that measurement of CRP in CSF could reliably differentiate pyogenic meningitis from non-pyogenic meningitis. But, there are very few studies supporting the same for our country. Hence, the present study was undertaken to evaluate the same.

**The findings of this study can be summarized as below:**

- The mean level of C-reactive protein in CSF was significantly higher in the pyogenic group as compared to non pyogenic group and control group which was statistically significant($p<0.001$).
- In this study, the mean CSF-CRP level in pyogenic group was 29.77mg/l as compared to non-pyogenic meningitis = 1.39mg/l, which was statistically significant (**$p < 0.001$).
- On comparing PM with NPM, the sensitivity and specificity of test was 90.0% and 100% respectively, with an accuracy of 95%. The Positive predictive value was 100% and NPV was 91% and p value was less than 0.001 which was statistically significant(**$p<0.001$)
- On comparing CSF-CRP values of PM with control group, the sensitivity and specificity was again 90% and 100% respectively with

an accuracy of 94%. The PPV and NPV in this case was 100% and 86.96% respectively and p value was less than 0.001 which was again statistically significant.

- In the pyogenic group the CSF-CRP level was noted to be higher in cases caused by Gram-negative organisms compared to Gram-positive organisms.
- Among the pyogenic group it was higher in those caused by Gram negative organisms = 35.77mg/l as compared to Gram positive organisms = 25.18mg/l
- In the non-pyogenic group CSF-CRP levels were slightly higher in the tubercular group as compared to viral meningitis and control group but it was not statistically significant.
- Among non pyogenic meningitis, CSF-CRP level was slightly higher in tuberculous meningitis = 1.50mg/l as compared to viral meningitis = 1.03mg/l but this was not statistically significant.

On the basis of above results, it can be concluded that CSF-CRP levels were significantly higher in pyogenic meningitis compared to non pyogenic meningitis and control group which was stastistically significant ( $P < 0.001$ ). Hence, the test is quite useful for differentiating PM from NPM as well as control but it cannot differentiate between TBM & VM. However, There are a number of limitations to this study as well:

- CRP production is a non-specific response to disease and it can never, on its own, be used as a diagnostic test. However, if the CRP result is interpreted in the light of full clinical information on the patient, then it can provide exceptionally useful information.
- Rises in CRP are only one part of a number of intricate changes in serum proteins, enzymes or CSF, but it happens to be one that is earliest to measure because it increases so dramatically. Hence, this can provide important clue for early differential diagnosis of the disease.
- Another problem is the impracticality of testing multiple samples of CSF as often as serum for monitoring response to treatment which favour the use of other investigations instead of CSF. Still, the procedure is inexpensive and suitable for use in endemic areas lacking sophisticated laboratory facilities.
- Next, the study group selected was small. To know accurate prognostic values, study on larger sampling is required. There were only 3 cases of fungal meningitis with CSF-CRP level in two of them being 5mg/l and in one case it was 4mg/l. But, these cases could not be included in the study as these patients were immunocompromised and were on ART therapy/steroids etc. Hence, a further study with adequate number of fungal meningitis cases is required.
- Although, the test was able to differentiate between pyogenic meningitis and non pyogenic meningitis but it could not differentiate between tuberculous and viral meningitis. Hence, a further study with larger number of TBM cases and VM cases, with better lab facilities for diagnosing Viral meningitis is required.
- Further, the cut off value for CSF-CRP positive test was taken as 6mg/l. CSF-CRP value of fungal meningitis & three cases of pyogenic meningitis were nearer to this value and were termed negative CSF-CRP. On lowering this cut off value and including larger group the sensitivity of the test can be increased further to a higher value.

Still, the present study has put forward to a number of avenues for future research. If the limitations are overcome, we would have strong guidelines for an early and efficient prognostic marker for differential diagnosis of meningitis.

To conclude, a diligent attempt to identify and culture organisms cannot be overlooked and still remains the gold standard test. But, for early diagnosis detection of C-Reactive protein in CSF

is suggested as a rapid, diagnostic, easy to do test for differentiating pyogenic meningitis from non-pyogenic meningitis.

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