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To Estimate the Diagnostic value of CSF CRP and Serum CRP levels in Clinically Defined/Suspected Cases of Meningitis

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Abstract

Context: Prognosis of meningitis depends on early diagnosis and initiation of and treatment. The role of CSF markers like CRP needs to be evaluated in diagnosis of infectious meningitis.

Aims: To evaluate the diagnostic significance of CSF CRP and Serum CRP in cases of infectious meningitis

Methods Settings and Design: This was prospective clinical study which included the clinical evaluation and routine CSF analysis including CSF CRP and Serum CRP levels of 50 cases of meningitis and 50 other control patients.

Statistical Analysis used: Analysis of data was done using SPSS-17. Independent t-test and chi-square test were used to calculate difference between two groups

Results: Our study showed that sensitivity of CSF CRP for bacterial, viral and tubercular meningitis was 88.8%, 10% and 9% respectively where as sensitivity of Serum CRP in bacterial, viral and tubercular meningitis was 100%, 10% and 90.9% respectively.

Conclusions: Our findings suggest that CSF CRP is highly specific to diffrentiate pyogenic meningitis from tubercular and viral meningitis. We also recommend doing serum CRP along with CSF CRP to diagnose and differentiate pyogenic and tubercular meningitis from viral meningitis

Keywords: C Reactive protein (CRP); Cerebrospinal fluid (CSF); Meningitis.

Key Messages: CSF and serum CRP levels are helpful in diagnosing cases of infectious meningitis.

INTRODUCTION

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.[1]

Meningitis is a potentially fatal inflammation of the meninges, the thin, membranous coverings of the brain and the spinal cord. In the decade from 1990 to 2010, an estimated global figure of approximately 420,000 deaths were associated with meningitis.[2] Bacteria meningitis occurs in about 3 per 100,000 population annually in the Western countries.[3] Meningitis continues to be a formidable illness with high morbidity and mortality in India.[4]

The causes of meningitis may be broadly classified as infectious (bacterial, viral, fungal and noninfectious (cancer related, SLE, drug induced). The most common types of meningitis are pyogenic (bacterial meningitis and tuberculous meningitis (TBM) The most common bacterial pathogens are Streptococcus pneumoniae, Neisseria meningitis and Staphylococcus aureus.

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Tuberculous meningitis is caused by Mycobacterium tuberculosis. Among the viral infections, the common causative organisms include the enterovirus and the Herpes simplex virus. Fungal meningitis is relatively uncommon and results in chronic meningitis.[3]

Nonetheless, specific pathogens to be identified are influenced by the age and immune status of the host and epidemiology of the pathogen.[5] The evolutionof clinical signs and symptoms produced by meningitis or encephalitis varies greatly.

These distinct clinical syndromes include acute bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess, subdural empyema. Each may present with a non-specific prodrome of fever and headache followed by altered sensorium, focal neurological signs and seizures may appear.[1]

The major problem presented by patients with meningitis is rapid determination of its aetiology. The examination of cerebrospinal fluid is an essential and often critical tool in the evaluation and management of patients with meningitis.

Smear and/or culture for AFB, smear and culture for bacteria, India ink preparation, latex agglutination for antigens of bacteria or cyptococci remain the gold standard for diagnosis of various etiologies of meningitis.

However, some of these tests especially for TBM and pyogenic meningitis can take time and may turn out negative. This is when physicians are in a diagnostic dilemma. Many patients are needlessly receiving antitubercular treatment and antibiotics in high doses on erroneous interpretation of CSF.[6]

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. C-reactive protein (CRP) is the classic acute phase reactant.[7] CRP levels in serum and cerebrospinal fluid (CSF) have been shown to be increased as a result of invasive central nervous system infection.[8] Isolation of aetiological agent by culture is a time consuming process while estimation of CRP is a rapid diagnostic procedure.[9]

However, the role of various cerebrospinal fluid (CSF) markers needs to be evaluated as not enough work has been carried out. It is in this context that the present study is planned to evaluate the diagnostic significance of cerebrospinal fluid CRP and Serum CRP in cases of infectious meningitis.

SUBJECTS AND METHODS

Aims and Objectives

- To estimate the diagnostic value of C-reactive protein (CRP) in serum and CSF in suspected cases of infectious meningitis
- To estimate the sensitivity, specificity, Positive Predictive Value, Negative Predictive Value of C-reactive protein (CRP) in serum and CSF in suspected cases of infectious meningitis.

MATERIALS AND METHODS

This study was conducted in Department of Neurology, Government Medical College, Kota for period of one year after getting clearance from ethical committee. Subjects were included from adult subjects attending Neurology OPD and IPD. All patients were included after written informed consent.

Study Population

The study included the clinical evaluation and CSF analysis of 50 cases of meningitis and 50 other patients were taken as controls on whom lumbar puncture was done performed for various other surgical procedures.

Study design

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

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 brain imaging in the form of CT scan was performed first and thereafter lumbar puncture was performed.

EXCLUSION CRITERIA

- Above 18 years of age
- Patients with history suggestive of meningitis presenting within 7 days of symptom onset
- Neck rigidity

All cases which had the following history will be excluded from study in order to avoid false positive

S-CRP results.

- Recent injury of any kind.
- Recent surgery.
- Patient in immediate postpartum period.
- Known case of Rheumatic heart disease (According to modified Jones criteria).
- Known case of Rheumatoid arthritis (According to ARA diagnostic criteria).
- Known case of acute or chronic Glomerular nephritis.
- All cases of Genito-urinary tract infection.
- Focal infections like pneumonic consolidation infection of skin etc.
- Causes for meningism like subarachinoid haemorr.

Criteria for Diagnosing different types of Meningitis

PM Group: CSF analysis showed marked decrease in glucose content, Moderate to marked elevation of protein, Marked elevation of cells predominantly polymorphs. Additionaly gram staining and culture was also done.

TBM Group: Criteria of diagnosis of these cases were biochemical analysis of CSF and raised CSF leukocyte counts with lymphocytic predominance, CSF AFB staining and AFB culture corroborated by history, clinical examination, positive Monteux test, suggestive x-ray and ct findings and others like CSF ADA.

VM Group: Diagnosis based on CSF leukocyte counts 25-500 cells/Cumm with lymphocytic predominance, normal CSF sugar, normal or marginally raised CSF protein, negative CSF gram and AFB staining, and CSF and blood culture

Serum and CSF CRP Determination

Serum and CSF CRP determination was done by latex agglutination slide test as per instructions of manufacturer. Test was based on principle of agglutination of anti CRP antibody coated polystyrene latex particles by bacterial antigen.

STATISTICAL ANALYSIS

Analysis of data was done using SPSS-17. For the categorical (qualitative) variables, frequency and percentage were calculated. Mean and standard deviation (SD) were calculated for numerical (quantitative) variables. $p<0.05$ was taken as significant. Independent t-test and chi-square test were used to calculate difference between two groups. The number of true positives (TP), true negatives (TN), false positive (FP), and false negative (FN). Sensitivity was the calculated as TP/(TP+FN), specificity as TN/(TN+FP), positive predictive values (PPV) as TP/(TP+FP) and negative predictive value (NPV) as TN/(FN+TN).

RESULTS

In our study Mean Age of control group was 40.2±14.43. In case of tubercular, viral and bacterial it was 37.9±16.66, 42.6±17.39, 38.77±14.00 respectively. In our study, Male:female in control group was 1.9: 1. In tubercular(1.75:1), viral(1.5:1) and bacterial(1:1) was seen.

Mean protein in CSF was 23.98±5.93 in control group. In tubercular, viral and bacterial it was 111.53±4.23, 67.89±32.56, 287.27±111.77 respectively. Mean protein in blood sugar (mg/dl) was 101.4±43.58 in control group. In tubercular, viral and bacterial it was 52.9±13.95, 93.2±19.75, 27.38±3.79 respectively.

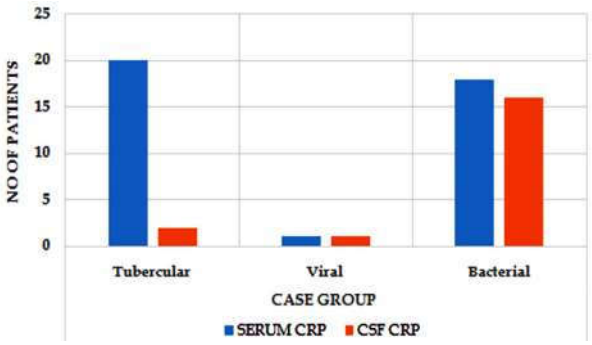
Mean Sugar CSF/Blood glucose was in blood sugar(mg/dl) was 0.84±0.07 in control group. In tubercular group it was 0.48±0.16(<0.5), in viral it was 0.82±0.04, in bacterial group it was 0.25±0.05(<0.5). Mean Cell count was 3.52±2.28 in control group. In tubercular, viral and bacterial it was 288.38±123.52, 5.9±3.10, 465.9±275.36 respectively.

Our study shows that Culture was negative in 100% patients in Tubercular patients, while it was negative in 88.8% of patients. Only 11.11% patient had positive culture in bacterial group. CBNATT was positive in 46.6% of patients and negative in 68.18% patiuents. Gram stain was positive in 55.55% in patients but negative in 44.44% of patients. AFB stain was negative in all tubercular patients.

Our study shows Serum CRP has a sensitivity of 90.9%, 10%,100% in tubercular,viral and bacterial group respectively. In case of CSF CRP it was 9.1%, 10% and 77% respectively. (Table 1, Graph 1) Our study shows Mean Serum CRP 3.34±1.39(mg/dl) in control group. It was 123.6±45.77, 23.44±9.47, 3.03±2.91 in tubercular, viral and bacterial group respectively.

Table 1: Senstivity of Serum and CSF CRP.

Specimen	Case Group					
	Tubercular		Viral		Bacterial	
	No.	%	No.	%	No.	%
Serum CRP	20	90.9	1	10	18	100
CSF CRP	2	9.1	1	10	16	77

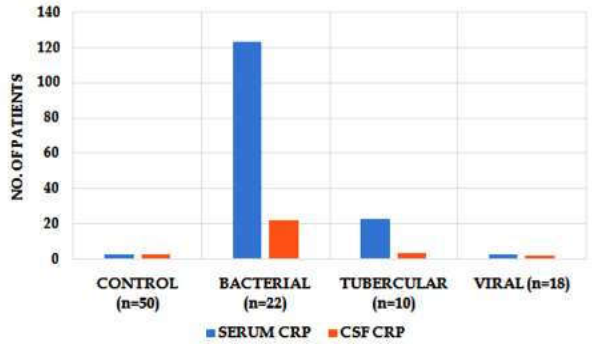


Graph 1: Senstivity of Serum and CSF CRP

In case of CSF, Mean CRP was 3.31±1.31 (mg/dl). In case of tubercular, viral and bacterial group it was 22.61±12.13, 3.94±0.18, 2.47±2.40 respectively. (Table 2, Graph 2)

Table 2: Mean for CRP in CSF and Ser.

Specimen	Control (n=50)	Bacterial (n=22)	Tubercular (n=10)	Viral (n=18)
Serum CRP	3.34±1.39	123.6±45.77	23.44±9.47	3.03±2.91
CSF CRP	3.31±1.31	22.61±12.13	3.94±0.18	2.47±2.40



Graph 2: Mean for CRP in CSF and Serum.

Our study shows that in case of Serum CRP, P value was significant in bacterial and tubercular group as compared to control but it was non significant in viral group as compared to control and also for bacterial-tubercular, bacterial viral and tubercular viral. In case of CSF CRP, it was significant for bacterial group vs control group as well as for bacterial vs tubercular and bacterial vs viral group. P value was non significant for tubercular vs viral

Our study shows that in case of Serum CRP, bacterial, viral and tubercular shows sensitivity of 100%,10% and 90.9% respectively. Specificity for bacterial, viral and tubercular group was 34.37%, 5%, 32.4% respectively. PPV was 46.15%, 2.56%, 51.28% for bacterial, viral and tubercular group respectively. NPV was 100%, 18.18%, 81.81% for bacterial, viral and tubercular group respectively. (Table 3)

Table 3: Sensitivity, Specificity, PPV, NPV in Serum CRP.

Group	Sensitivity	Specificity	PPV	NPV
Bacterial	100	34.37	46.15	100
Virus	10	5	2.56	18.18
Tubercular	90.9	32.40	51.28	81.81

Our study shows that in case of CSF CRP, bacterial, viral and tubercular shows sensitivity of 88.8%, 10% and 9% respectively. Specificity for bacterial, viral and tubercular group was 90.62%, 55%, 39.4% respectively. PPV was 84.21%, 9.5 %, 10.52% for bacterial, viral and tubercular group respectively. NPV was 94.54%, 70.96%, 35.48% for bacterial, viral and tubercular group respectively. (Table 4)

Table 4: Sensitivity, Specificity, PPV, NPV in CSF-CRP.

Group	Sensitivity	Specificity	PPV	NPV
Bacterial	88.8	90.62	84.21	93.54
Virus	10	55	9.5	70.96
Tubercular	9	39	10.52	35.48

DISCUSSION

CNS infections like meningitis needs urgent treatment intervention considering the high mortality rates which are associated with it and also keeping in mind the resulting neurological sequale which can adversaly affect the quality of life of the patient. Due to clinical dilemma which is involved in the acute cases of meningitis and also the sometimes overlapping picture in CSF, treatment often gets delayed which can be catastrophic. In this regard, C reactive protein level can be used as rapid tests in differential diagnosis of meningitis The present study revealed that CSF CRP qualitative test had sensitivity of 88.8% in PM group. Studies done by Ramchandani et al[10] (83.33%), Kishore R et al[11] (85.7%), Mishra O.P. et al[12] (75%), had similar results. Study by Ahmed P et al[13], Vaidya A.K. et al[14], Singh UK[15] et al and Macfarlane D.E. et al.[16] showed 100% positive results. However Finley F.O. et al[17] (58%), Przyjalkowski W. et al[18] (62.5%), Kaldor J. et al[19] (62.26%), Benjamin D.R. et al[20] (66%) found less sensitivity. Present study revealed that CSF CRP qualitative test had 9% sensitivity in TBM group. Similar observations were reported by Kishore R et al[11] which had sensitivity of and 11.23%, respectively in TBM group. In our study we also found that CSF CRP qualitative test had 9% sensitivity in VM group. Similar studies by Benjamin D.R. et al[20] showed 12.5% sensitivity of test in VM group, respectively. Observations reported by Donald

P.R. et al[21], Abrahmson J.S. et al[22], Vaidya A.K. et al[14] had 0% sensitivity. Our study showed that CSF CRP was significantly raised (p<0.001) in PM group in comparison to TBM group. Ramchandani et al[10], Ahmed p. et al[13] and Donald P. et al[21] made similar observations. However Vaidya A.K. et al[14] showed that levels were not significant (p>0.05) in PM group in comparison to TBM group. Present study showed that CSF CRP was significantly raised (p<0.001) in PM group in comparison to VM group. Similar observation was reported by Ramchandani et al[10], Singh U.K. et al[15], Vaidya A.K. et al[14] and Ahmed P. et al.[13] Our study also showed that CSF CRP was not significant (p>0.05) in TBM group in comparison to VM group. Similar observations were reported by Ahmed et al.[13] However, Vaidya A.K.[14] and Donald P.R. et al.[21] showed that levels were highly significant (p<0.001) in TBM group in comparison to VM group. In present study serum CRP Qualitative Test was positive in both PM and TBM group with sensitivity of 100% and 90.9% respectively. Similar observations were found in both PM and TBM groups by Sutinen J. et al,[23] Przyjalkowski W. et al,[18] Petola H. et al[24] and Debeer F.C. et al.[25] In present study serum CRP qualitative test showed 10% sensitivity in VM group. Similarly, Sormunnen P. et al[26] showed 7% sensitivity of test in VM group. However results observed by Paltola H. al.[24], ramchandani et al[10] had 0% sensitivity. We also found that Serum CRP level were not significantly raised (p>0.05) in PM group in comparison to TBM group. Ahmed P. et al[13] and Debeer F.C. et al[25], ramchandani et al[10] showed similar results reported similar observations. Present study showed that serum CRP levels were significantly raised (p<0.001) in PM group in comparison to VM group. Ahmed P. et al[13], Peltola H. et al[24], Benjamin D.R. et al[20] and Debeer F.C. et al[25] showed similar observations. Higher CRP levels in CSF and serum could be due to greater inflammatory response induced by pyogenic infection than by tubercular and viral infections, as bacteria has extracellular life cycle compared with predominant intracellular life cycle of virus.[27]

Present study observes PPV, NPV of 46.15 and 100% of serum CRP in PM group and PPV and NPV of 84.21% and 93.54% in CSF CRP in PM group. This study showed PPV, NPV of 2.56% and 18.8% of serum CRP in VM group and PPV and NPV of 9.5% and 70.96% in CSF CRP in VM group. Present study showed PPV, NPV of 51.28% and 81.81% of serum CRP in TBM group and PPV and NPV of 10.52% and 35.48% in CSF CRP in VM group. Similar observations were seen in studies by Siddiqui et al.[1] which compared Sensitivity, Specificity, Positive predictive value and Negative predictive value in differentiating Bacterial meningitis from non-Bacterial meningitis.

LIMITATIONS

Our study has few limitations. Due to lack of resources we didn't do PCR for confirmation of viral meningitis. As the sensitivity of CBNAAT and AFB stain for diagnosis of Tubercular meningitis is low, diagnosis of TB meningitis in some cases was made with help of other ancillary tests like Chest Xray, Neuroimaging collaborated with History and examination. Secondly, our sample size was also small.

CONCLUSION

Our findings suggest that CSF CRP is highly specific to diffrentiate pyogenic meningitis from tubercular and viral meningitis. We also recommend doing serum CRP along with CSF CRP to diagnose and differentiate pyogenic and tubercular meningitis from viral meningitis. Hence, C reactive protein level can be considered as reliable, cost effective, rapid diagnostic test which can be used to differentiate various types of infectious meningitis in acute stages, especially in those cases where clinical dilemma exists and routine CSF studies are overlapping.

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