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ORIGINAL ARTICLE

To evaluate the CSF C-reactive protein in meningitis to differentiate bacterial meningitis from aseptic meningitis in children

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ABSTRACT:

Aim: To evaluate the CSF C-reactive protein in meningitis to differentiate bacterial meningitis from aseptic meningitis in children.

Methods: The Prospective, Observational study was conducted in the Department of pediatrics. 130 children between 1 month to 12 years of age admitted with acute history of fever and seizure were included in the study. Patients were divided into 3 groups based on clinical and CSF findings. Group 1 (Bacterial meningitis) was defined by a CSF leukocyte count of 100–10,000/mm^3 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^3 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.

Results: During the study period 130 patients were enrolled in our study after written informed consent was obtained. 85(65.38% of our cases were males. The mean age of our cases was 76.25±42.69 months. Depending on the CSF cytology, biochemistry and bacteriology 50 cases had bacterial meningitis and were included in Group 1, 45 cases had Aseptic Meningitis and were included in Group 2 and 35 cases had no meningitis hence included in Group 3. CSF-CRP was positive in 36 (72%) cases of Bacterial meningitis, 7(15.56%) cases of aseptic meningitis and negative in all cases of control group. The Sensitivity 73.26%, Specificity 86.87%, Positive Predictive Value (PPV) 85.98%, Negative Predictive Value (NPV)74.77% and Diagnostic Accuracy (DA) 80.28% of CSF-CRP for diagnosis of bacterial meningitis.

Conclusion: We concluded 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.

Keywords: CSF, CRP, Bacterial Meningitis

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INTRODUCTION

Meningitis is one of the major cause of non-traumatic coma in children.[1,2] In India, the rate of meningitis in children aged 1 to 24 months was 27.4% with 12.4% cases being bacterial meningitis.[2] The risk of morbidity and mortality in children is high with those <5 years having doubled risk than those >5 years of age.[3] The diagnosis and management of childhood meningitis is challenging at primary and secondary health care level that adds to the increased risk of complications arising from delayed referral to tertiary care centre.

The diagnosis of meningitis is based on the documentation of an inflammatory response in the CSF along with additional tests that identify specific causative agents in the CSF. As prior antibiotic therapy can affect the bacteriological diagnosis from CSF (Gram stain and culture may be negative in up to 80% cases), and culture facility is not available at primary and secondary health care level, rapid bedside diagnostic tests like measurement of CSF CRP (latex agglutination or immunoturbidometric method) have been used in various studies.[4-8] CRP is an acute phase protein, the level of which is increased, in the blood and various other body fluids as a response to various non-specific stimuli (e.g., infection, inflammation, or tissue necrosis).[9] It is also found to be a useful test in the diagnosis of partially treated pyogenic meningitis where CSF biochemical and cytological values may be equivocal.

In a recent study from Nepal, CSF CRP had a sensitivity and specificity of 96.87% and 74.73% for pyogenic meningitis; 66.66%, and 63.71% for partially treated meningitis; 20.58% and 50.94% for viral meningitis; 10% and 55.38% for tubercular meningitis, respectively.[4] In a study from India, CSF CRP test detected 80% cases of pyogenic meningitis, 15% cases of tubercular meningitis, and was negative in those without meningitis. The positive predictive value of the test for pyogenic and tubercular meningitis was 100%.[7]

MATERIAL AND METHODS

The Prospective, Observational study was conducted in the Department of pediatrics, after taking the approval of the protocol review committee and institutional ethics committee. 130 children between 1 month to 12 years of age admitted with acute history of fever and seizure were included in the study. 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 lumber 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.[10] Group 1 (Bacterial meningitis) was defined by a CSF leukocyte count of 100–10,000/mm^3 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^3 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 21.0. 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 130 patients were enrolled in our study after written informed consent was obtained. 85(65.38% of our cases were males. The mean age of our cases was 76.25±42.69 months (Range 3-135 months).

Depending on the CSF cytology, biochemistry and bacteriology 50 cases had bacterial meningitis and were included in Group 1, 45 cases had Aseptic Meningitis and were included in Group 2 and 35 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	Group 2	Group 3
	n=50	n=45	n=35
Total WBC (mm^3) Range (Mean)	109 - 18,500 (7115)	39 - 475 (241)	0-5 (2.5)
PMN (%) range (mean)	58 - 91(71)	0 - 43 (18)	0 (0)
Protein (mg/dl) range (mean)	111-574 (269)	55 - 198 (111)	17 - 41 (21)
Glucose (mg/dl) Range (mean)	(10-69) (23)	35 - 77 (59)	55 - 79 (68)
CSF-CRP (positive)	36(72%)	7(15.56%)	0

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

Table 2: Organisms isolated in the bacterial meningitis group

Organism	N	%
S. pneumonia	21	42
H. influenza	18	36
N. meningitides	8	16
E. coli	3	6
Total	50	100

CSF-CRP was positive in 36 (72%) cases of Bacterial meningitis, 7(15.56%) cases of aseptic meningitis and negative in all cases of control group.

Hence the Sensitivity 73.26%, Specificity 86.87%, Positive Predictive Value (PPV) 85.98%, Negative Predictive Value (NPV)74.77% and Diagnostic Accuracy (DA) 80.28% of CSF-CRP for diagnosis of bacterial meningitis

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	11
Not-Cured	24	3
Total	36	14

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 = 7.39 with 1 degree of freedom; P = 0.007).

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 36 (72%) cases of Bacterial meningitis, 7 (15.56%) 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.[11] John M et al also in their study reported that 91% of the case of bacterial meningitis were CSF-CRP positive.[12] 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 tose with aseptic meningitis.[13] However, Khanam R had reported only 35% of bacterial meningitis cases to be CSF-CRP positive.[14]

Our study reported the CSF-CRP to have the Sensitivity 73.26%, Specificity 86.87%, Positive Predictive Value (PPV) 85.98%, Negative Predictive Value (NPV)74.77% and Diagnostic Accuracy (DA) 80.28% of CSF-CRP for diagnosis of bacterial meningitis

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%.[11] Pemde HK et al in their study reported that CSF CRP test showed 100% sensitivity and negative be predictive values, 95- 100% specificity and 94-100% positive predictive values.[15] 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.[14]

CRP migration to CSF is not properly explained in literature. CSF-CRP levels were fund 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.[16] 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.[17] 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.[14]

CONCLUSION

We concluded 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.

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