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Study of CSF C-Reactive Protein for the Differentiation of Bacterial Meningitis from Aseptic Meningitis in Children

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Abstract **Original Research Article**

Background: Acute meningitis is a major cause of death, and disability worldwide. Differentiating bacterial from nonbacterial meningitis is very important in deciding on treatment. Bacterial meningitis is a life-threatening neurological condition, and needs prompt parenteral antibiotics, compared to viral, and aseptic meningitis which carries relatively better outcomes. ***Objective:*** To identify the importance of Cerebrospinal fluid C- reactive protein (CSF-CRP) to establish the diagnosis of ABM. ***Method:*** This study was conducted from 01 January 2017 to 30th June 2017 at the indoor department of Pediatric Medicine at Bangladesh Sishu Hospital & Institute (BSH & I) to the measure of CSF C-Reactive protein for the differentiation of bacterial meningitis from aseptic meningitis in children. One hundred patients had participated after meeting the inclusion, and exclusion criteria. Patients were selected by purposive sampling. Ethical clearance was obtained from the National Health Research Ethics Committee, BangladeshShishu Hospital& Institute, Dhaka. ***Results:*** Out of 57 cases of bacterial meningitis, 22 cases were culture-negative, and 35 cases were culture-positive. 22 cases (62.85%) out of 35 cases culture positive were Streptococcus Pneumoniae followed by 08 cases (22.85%) were Neisseria Meningitis, Haemophilus Influenza 3 cases (8.57%), E.coli were 02 cases (5.71%). WBC count & PMN (%) were increased significantly in bacterial meningitis, compared to aseptic meningitis. Protein and glucose levels in CSF were not significantly different between bacterial meningitis, and the aseptic meningitis group (Table 2). In the case of bacterial meningitis, in 51(89.47%) cases out of 57, the CSF CRP test was truly positive, mean±SD 21.7±10.9, and false negative were only 6 cases (10.52%). In aseptic meningitis 39 cases (90.69%) out of 43 cases, the CSF-CRP test was truly negative, and false positives were 04 cases (9.30%). (Table-4) shows outcome in the meningitis group showed that only 36 cases (65.45%) out of 55 cases were cured with CSF-CRP positive cases, with the worse outcome as compared to CSF-CRP negative cases, 39(86.66%) cases were cured out of 45 cases (P =0.0001). ***Conclusion:*** Our study is to assess the role of serum inflammatory markers CRP, and routine CSF analysis in the rapid diagnosis and differentiation of acute bacterial meningitis from aseptic meningitis to reach a cost-effective diagnostic approach based on routine diagnostic tools.

Keywords: Bacterial, Aseptic, Meningitis, Protein, CSF.

INTRODUCTION

Meningitis is one of the potentially serious infections occurring in infants, and older children, and is an important cause of mortality, and morbidity. Acute bacterial meningitis is a pediatric emergency that needs early diagnosis, and prompt treatment to avoid complications. Often differentiation of bacterial meningitis from aseptic meningitis is difficult. Determination of some inflammatory mediators like IL-6, and CRP was useful in the differential diagnosis of bacterial, and aseptic meningitis [1]. Case fatality rates for bacterial meningitis range from 4.5% in developed countries to 15–50% in developing countries.[2] A further 15–20% of survivors sustain neurological sequelae.[3] The mortality from meningitis is close to 100% in untreated individuals, and can still be up to 40% in children who received appropriate antibiotic therapy in developing countries [2, 3]. Rapid, and accurate diagnosis coupled with early appropriate therapy is of

most importance in reducing morbidity, and mortality of the patients [4]. Culture and sensitivity, Gram stain, cytology, and biochemistry of cerebrospinal fluid (CSF) sample are traditionally done to diagnose and to differentiate pyogenic from aseptic meningitis. Prior antibiotic therapy, transportation delays, and inoculation all have an impact on proper culture. The organism must be isolated for more than 24 hours. Gram stain is nonspecific and has interpretative flaws [5]. LAT was more sensitive than the conventional Gram stain and Culture technique in identifying fastidious organisms such as H.Influenzae, S.Pneumoniae, and Group B Streptococcus, but it is expensive and only available in certain areas. The combination of Gram stain, Culture, and LAT, on the other hand, proved to be more productive than any of the individual tests. Blood or CSF analysis cannot distinguish all cases of aseptic from bacterial meningitis in young children with meningitis. Pleocytosis is a poor prognostic sign in patients with severe overwhelming sepsis. Conversely, Neutrophilic pleocytosis may be present in patients during the early stage of aseptic meningitis which makes the patient receive expensive antibiotics for a prolonged period causing financial burden, and prolongation of hospital stay. In such circumstances, an Easy, and early diagnostic tool is required for the rapid detection of bacterial meningitis to reduce mortality and morbidity. The detection of C-reactive protein in CSF appears to provide a new dimension. Its presence in significant amounts in CSF favors the diagnosis of acute bacterial meningitis and predicted the possibilities of treatment. The aim of the study is to identify the importance of measurement of CSF-CRP for differentiating Acute bacterial meningitis from aseptic meningitis in children.

MATERIALS & METHODS

This cross-sectional observational study was carried out in the Pediatric Medicine Department, Dhaka Shishu (Children) Hospital over the period of 2 years, from 01 January 2017 to 31 December 2018. Around 140 children admitted between the age of 0-12 years with fever with convulsion, and clinically diagnosed with meningitis has included in this study. This data-based study was done after taking proper permission from the concerned departments, and the local ethical committee for the fulfillment of the requirements for the dissertation of the FCPS (Part II) Examination of Bangladesh College of Physicians, and Surgeons (BCPS). Under strict aseptic precautions, 2ml of CSF specimen was collected and sent for analysis (cytology, biochemistry, gram staining, and culture). Patients who received antibiotics before admission, who had normal CSF findings and those who refused to do CSF analysis were excluded from this study. Finally, 100 patients who were diagnosed with meningitis were divided into two groups: Bacterial Meningitis (CSF WBC count 100-10,000/cumm with PMN predominance, increased CSF Protein count 100-500mg/dl & markedly reduced glucose,40mg/dl), and Aseptic Meningitis (CSF WBC count 10-100/cumm with lymphocyte predominance, glucose generally normal, protein count raised 50-200mg/dl). CSF-CRP measurement was done by Latex Agglutination Test. Data were analyzed by using the SPSS software, version 20.0. Categorical data were presented as frequency, percentage, and the continuous variable was expressed as mean±SD (standard deviation). An independent sample Student's t-test was used for the comparison of means of continuous variables with normal or approximately normal distributions. The Fisher exact test has been used to analyze discrete variables. The statistical significance threshold was set to $p \leq 0.05$ (two-tailed). The confidence interval was set at a 95% level.

RESULTS

Out of 100 cases examined, most of them (43%) are below 2yrs of age (Fig 1); 1/3rd of bacterial meningitis occurred commonly at an early age (below 2yrs), and aseptic meningitis commonly occurred above 2yrs of age (Fig 2). Out of 57 cases of bacterial meningitis, 35 cases were culture-positive. The pathogens identified in the blood culture were: S.Pneumoniae (17), H.Influenza (6), N. Meningitidis(10) E.Coli (2) (Table 1). Also, the study shows out of 57cases of bacterial meningitis 51 are CSF-CRP positive, and only 4 cases out of 43 aseptic cases are CSF-CRP positive (Table 3). Among the positive cases, only 36cases (65.45%) out of 55were cured, the remaining experienced worse outcome as compared to CSF-CRP negative cases 39 (86.60%) were cured out of 45 cases (Table 4).

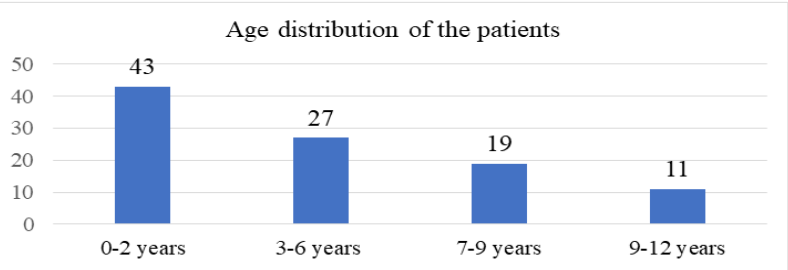

Figure 1: Age distribution of the participants (n=100)

Fig 1 shows that most of the patients (43%) were 0-2 years of age.

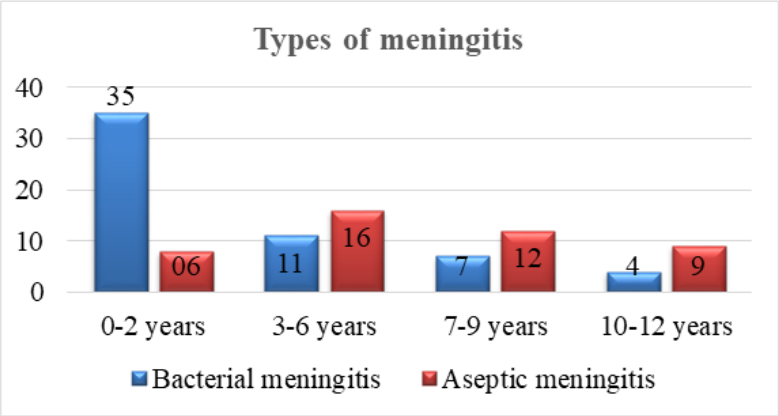

Figure 2: Types of meningitis according to age (n=100)

Figure 2 shows that 1/3rd of bacterial meningitis 35(35%) occurs commonly at an early age (0-2 years), 11 (11%) in 3-6 years, 7% at 7-9 years of age, 4% at 10-12 years of age, and aseptic meningitis commonly occurs after 2 years of age. 16% at 3-6 years of age, 12% at 7-9 years, and 9% at 10-12 years.

Table 1: Bivariate distribution of aetiopathogenesis of ABM according to age (n=57)

Organism found (n=35)	0-2 years (n=22)	3-6 years (n=08)	7-9 years (n=03)	10-12 years (n=02)
S. pneumoniae	10(45.45%)	05(62.5%)	01(33.33%)	01(50%)
H. influenzae	6(27.27%)	00	00	00
N. meningitidis	04(18.18%)	03(37.5%)	02(66.66%)	01(50%)
E. coli	02(9.09%)	00	00	00
Organism not found (n=22)	-	-	-	-
Total=57	22	08	03	02

Table 1 shows that out of 57 cases of bacterial meningitis, 22 cases were culture-negative, and 35 cases were culture-positive. 22 cases (62.85%) out of 35 cases were streptococcus pneumoniae followed by 08 cases (22.85%) were Neisseria meningitis, Haemophilus influenza 3 cases (8.57%), E.coli were 02 cases (5.71%).

Table 2: Laboratory Characteristics of CSF in studied patients (n=100)

Parameters	Bacterial meningitis (n=57)	Aseptic Meningitis (n=43)	P value
Total WBC (mm^3)	(Mean) 70 – 22,000 (5021)	Range (Mean) 38 – 520 (158)	0.001
PMN (%)	(Mean) 64 – 97(85)	(Mean) 0 – 56 (21)	0.01
Protein (mg/dl)	(Mean) 104 – 597 (316)	(Mean) 48 – 300 (112)	0.07
Glucose (mg/dl)	(Mean) 7 – 75 (28)	(Mean) 33 – 77 (54)	0.08

*P value from t-test calculator

Table 2 shows that WBC count & PMN (%) were increased significantly in bacterial meningitis, the mean WBC count among bacterial meningitis cases was 5021 mm^3, 85% higher compared to aseptic meningitis which was only 158 mm^3.

Table 3: CSF C-Reactive Protein test results in study subjects (n=100)

CSF CRP Test Results	Bacterial meningitis (n=57)		Aseptic meningitis (n=43)		P value
	Number	Mean±SD	Number	Mean±SD	<0.0001
CRP Positive	51	21.7±10.9	04	2.1±1.2 06	
CRP Negative	06		39		
Total	**57**		**43**		

*P value from Fisher Exact Test

In the case of bacterial meningitis, in 51(89.47%) cases out of 57, the CSF CRP test was positive, with Mean±SD 21.7±10.9. In aseptic meningitis in 39 cases (90.69%) out of 43 cases, the CSF-CRP test was negative.

Table 4: Outcome in the meningitis group (n=100)

CRP	Outcome		P-value
	Cured	Not cured	
Positive (n=55)	36	19	**<.0001**
Negative (n=45)	39	06	
Total	75	25	

The outcome of meningitis cases is tabulated in Table 4. Cured was defined as improvement with no obvious sequel whereas not cured was defined as death or obvious sequel at end of treatment.

Table 4 shows that the outcome in the meningitis group was observed that only 36 cases (65.45%) out of 55 cases were cured with CSF-CRP positive cases, the worse outcome as compared to CSF-CRP negative cases 39(86.66%) cases were cured out of 45 cases (P = 0.0001).

DISCUSSION

Bacterial meningitis is a common serious illness during infancy, and childhood, and also is an important cause of mortality, and morbidity in children. Early recognition and initiation of treatment with the appropriate drug are crucial to avoid this situation. In a resource-limited country like Bangladesh where the appropriate isolation of organisms is difficult and time-consuming, an easy, quick, cheap, and reliable test is needed to diagnose the etiology of meningitis at the bedside. CSF-CRP is a test that meets all these criteria. Our study suggests that CSF CRP can be used in situations where the isolation of organisms is difficult. The result of this hospital-based study showed that infants were most vulnerable to acute bacterial meningitis Most of the patients (43%) were 0-2 years of age, Bacterial meningitis (35%) occurs commonly in this age group,.11% in 3-6 years, 7% at 7-9 years of age, 4% at 10-12 years of age, and aseptic meningitis commonly occurs after 2 years of age (Figure-2). Most of the organisms 62.85% were Streptococcus Pneumoniae followed by 22.85% Neisseria Meningitis, Haemophilus Influenza 8.57%, E.Coli were (5.71%). Similar observations were also reported by Khanam R *et al*., where Streptococcus Pneumoniae was the most common organism (66.7%) followed by Neisseria Meningitis, Haemophilus Influenza, and E.Coli [6]. In the present study, CSF-CRP was positive in 51 (89.47%) cases of Bacterial meningitis, 04 (6.97%) cases of aseptic meningitis. Bhagwan S *et al*., reported that 72.9% of cases of Bacterial Meningitis, and 14.3% of cases of aseptic meningitis had been CSF-CRP positive [7]. Jadavinia *et al*., reported a statistically significant higher level of CRP in CSF of patients with bacterial meningitis as compared to those with aseptic meningitis [8]. Malla KK *et al*., in their study had also reported a statistically significant higher level of CRP in CSF of patients with bacterial meningitis as compared to those with aseptic meningitis [9]. However, Khanam R had reported only 35% of bacterial meningitis cases to be CSF-CRP positive [6]. Bhagwan S *et al*., reported that CSF-CRP has 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.*** Jadavinia *et al*., in their study concluded that CSF-CRP had a sensitivity of 95%, specificity of 86%, and a positive predictive value of 100%. 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 [6]. Diffusion of serum albumin and globulin across the inflamed meninges has been demonstrated, and it seemed feasible that CRP may cross from serum to CSFin in a similar fashion. Passive diffusion across highly inflamed meninges would be a reasonable explanation as to how CRP gains access to CSF [10, 11]. Laboratory characteristics of CSF in patients with ABM showed neutrophilic leukocytosis. As expected, in aseptic meningitis CSF pleocytosis was at the lower range with lymphocytic predominance, and all the values were found within the normal range. CSF protein was elevated more in ABM than in aseptic meningitis. Expectedly, CSF glucose was much lower in ABM than that in aseptic meningitis. These findings were consistent with the findings of Prober CG [4]. CSF-CRP was measured by the semi-quantitative latex agglutination method where the cut-off value was equal to or more than 6 mg/L for observation of agglutination [10, 14]. In different studies CSF-CRP was positive in 66%, and 85%, where cut-off values for positive were at the level of >1mg/L, and >0.5mg/L respectively [15, 16]. CSF-CRP concentrations were several folds lower than those of serum. This difference was explained by the direct hepatic release of CRP into plasma which then undergoes ultra-filtration to form CSF [14]. 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. Suspected meningitis that subsequently demonstrates detectable CRP in CSF should be declared as bacterial meningitis [17]. In bacterial 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 [10]. Routine CSF examination can differentiate between ABM, and Aseptic meningitis but lacks precision. For better differentiation between ABM, and aseptic meningitis, predictive values were calculated between these two groups. In this study, the negative predictive value of CSF-CRP in ABM was 86.66% which was also sensitive (sensitivity-89.47%) to be useful for routine application for the diagnosis of ABM. On the contrary, the positive predictive value was 92.72%. It signifies that the presence of CRP in CSF strongly suggested the diagnosis of ABM, and ruled out aseptic meningitis. This observation was also familiar with the finding of Pemde HK *et al*., [10] CSF-CRP positive patients demonstrated significantly higher mortalities, and morbidities whereas; CSF-CRP negative patients had much higher recovery. This thoroughly highlighted the importance of the CSF-CRP level in ABM to be used as a bad prognostic criterion. The determination of CSF-CRP has a significant role in differentiating bacterial meningitis from aseptic meningitis. Its presence significantly favored, in this study, the diagnosis of acute bacterial meningitis, and predicted the possibility of a poor outcome of the treatment [18].

CONCLUSION

The study 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 while waiting for other confirmatory test results. The presence of reactive CRP in CSF could be considered a poor prognostic criterion, predicting a poor treatment outcome.

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