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Original Research Article

The Specificity, Sensitivity, and Diagnostic Accuracy of CSF-CRP in the Diagnosis of Acute Bacterial Meningitis- A Hospital-Based Study

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Abstract

Introduction: Bacteria that enter the bloodstream and mobile to the brain cord cause bacterial meningitis. The disease is less frequent in developed countries compared to developing countries. In Bangladesh, bacterial meningitis constitutes 25% and the case fatality rate was 14%. The mortality from meningitis is near 100% in untreated individuals and can still be up to 40% in children who received appropriate antibiotic therapy in developing countries. ***Aim of the Study:*** The study aims to investigate the specificity, sensitivity, and diagnostic accuracy of CSF-CRP in the diagnosis of Acute Bacterial Meningitis (ABM). ***Methods:*** An observational cross-sectional study was carried out in the Department of Pediatric Medicine, Dhaka Shishu Hospital (DSH), from 01 Jan-2017 to 30 Jun-2017. A total of 100 patients were enrolled in this study following the inclusive criteria. Data were collected using the predesigned semi-structured questionnaire. Verbal consent was taken before recruiting the study population. Completed data forms were reviewed, edited, and processed for computer data entry. ***Result:*** Among the study population majority of patients (43, 43.0%) were 0-2 years old. One-third of bacterial meningitis (35,35.0%) occurs commonly at an early age (0-2 years). Out of fifty-seven cases (n=57) of bacterial meningitis, twenty-two cases were culture negative and thirty-five cases were culture positive. In the case of bacterial meningitis, in fifty-one cases (51,89.4%) out of fifty-seven, the CSF CRP test was truly positive, with mean±SD 21.7±10.9, false negative were only six cases (6, 10.5%). In aseptic meningitis thirty-nine cases (39,90.6%) out of forty-three cases, the CSF-CRP test was truly negative, and false positive were four cases (4,9.3%). The sensitivity of CSF CRP in differentiating bacterial meningitis from aseptic meningitis was 89.47%, specificity 90.69%, & diagnostic accuracy was 90%. ***Conclusion:*** Bacterial meningitis is fatal and more communal in children under one year of age to sixteen years of age. Increased consciousness and initial gratitude and apposite antibiotic treatment can decrease morbidity and mortality. Diagnostic accuracy can be applied as the initial test for the diagnosis of bacterial meningitis.

Keywords: Bacterial Meningitis, CSF-CRP, Infants, Diagnostic Accuracy.

INTRODUCTION

Meningitis is a shattering disease with a high case fatality rate and foremost severe long-term complications. Meningitis is one of the most possibly serious infections occurring in infants, especially in neonates, and is a significant cause of morbidity and mortality [1]. The disease is less frequent in developed countries compared to developing countries. In Bangladesh, among all meningitis cases, bacterial meningitis constitutes 25% and the case fatality rate was 14% [2]. Half of the Bacterial meningitis survivors may develop neurological complications [3]. The advancement in lessening child mortality over the era of the United Nations (UN) Millennium Development Goals (MDGs) with an assessed 54% debility in children under five years of age from 93 deaths per 1000 live birth in 1990 to 43% per 1000 live birth in 2015 [4]. 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 [5]. Surveys in 2010 found that meningitis caused 422,900 deaths and 262,800 cases of neurological disorders [6]. Early detection and instant cure of meningitis are essential as their possible adverse effects. Gram staining is precisely obtainable and cost-effective and a rapid procedure is

performed for the primary diagnosis of bacterial meningitis [7]. But gram stating sensitivity is not reliable, so Cerebrospinal fluid (CSF) culture is mandatory to diagnose bacteria; meningitis [8]. Cerebrospinal fluid (CSF) cell count is a key sign in the diagnosis of bacterial meningitis and this type of presentation is extremely common in children [9]. CSF lactate is formed by bacterial anaerobic metabolism and is not affected by blood lactate concentration to improvise over CSF glucose in distinguishing bacterial meningitis from aseptic meningitis [10]. For several decades, serum C- reactive protein has been used to distinguish between bacterial and viral infections in industrialized countries [11]. In recent years it has been reported that the measurement of CRP in CSF is a dependable, sensitive, and easy test for quick diagnosis of meningitis [11-13]. Latex agglutination test (LAT) and other rapid diagnostic tests are available but costly and present only in the discerning part. Leukocyte count in bacterial meningitis may be raised to greater than 1000/mm3. Pleocytosis with a lymphocytic predominance may be present during the early stage of acute bacterial meningitis; conversely, neutrophilic pleocytosis may be present in patients during the early stages of acute viral meningitis [14]. Antibiotics make the gram stain and culture negative and may alter the CSF cytology from neutrophilic to lymphocytic predominance. Empirical antibiotic therapy is often given. In such circumstances, the finding of C-reactive protein in CSF appears to offer an innovative dimension to the diagnosis of meningitis [15]. This present analysis intends to identify the specificity, sensitivity, and diagnostic accuracy of CSF-CRP in the diagnosis of Acute Bacterial Meningitis (ABM).

OBJECTIVES

- To measure the specificity, sensitivity, and positive and negative predictive values of CSF-CRP in the diagnosis of Acute Bacterial Meningitis from Aseptic Meningitis.
- To identify the importance of cerebrospinal fluid C- reactive protein (CSF-CRP) to establish the diagnosis of ABM.

METHODS

An observational cross-sectional study was carried out in the Department of Pediatric Medicine, Dhaka Shishu Hospital (DSH), from 01 Jan-2017 to 30 Jun-2017. A total of 100 patients (N=100) from 0 to 12 years were enrolled in this study following the inclusive criteria. Data were collected using the predesigned semi-structured questionnaire. A purposive sampling technique was used. Ethical clearance was taken from the hospital. The information was kept confidential only to be used for the study purpose.

Inclusion Criteria

- All children admitted in the age group of 0-12years with fever and convulsion of short duration.
- The patients who had characteristics, signs & symptoms of meningitis & had not received any antibiotics prior to admission.
- Children with bacterial /aseptic meningitis were diagnosed based on CSF findings.

Exclusion Criteria

- Severely ill patient.
- Meningitis in patients suffering from other systemic illnesses (such as cardiac, kidney diseases, severe acute malnutrition, etc).
- After doing LP if a pt fails to fulfill the criteria of bacterial or aseptic meningitis according to the operational definition.
- Parents of a pt who would not give consent to doing LP to their children.

Operational Definition

- **Bacterial Meningitis:** In this study, only those cases were included who's CSF WBC count was between 1000- 10,000 /cumm or more with PMN predominance & also increased CSF Protein count (usually 200-500mg/dl) & markedly reduced glucose (<40mg/dl)
- **Aseptic Meningitis:** Only those patients included in this group whose CSF WBC count rarely >1000/cumm with lymphocytic predominance, glucose generally normal (maybe <40mg/dl) protein count raised (50-200mg/dl).

Data Analysis

The study coordinators performed random checks to verify data collection processes. Completed data forms were reviewed, edited, and processed for computer data entry. Frequencies, percentages, and cross-tabulations were used for descriptive analysis. A simple statistical method was applied. ANOVA test and *t-test* were performed.

RESULTS

Among the study population majority of patients (43, 43.0%) were 0-2 years old & around one-fourth (27, 27.0%) of the children aged 3 to 6 years old. Most of the children (60, 60.0%) were male. One-third of bacterial meningitis (35,35.0%) occurs commonly in early age (0-2 years), eleven (11,11.0%) at 3-6 years, seven (7, 7.0%) at 7-9 years of age, four (4,4.0%) at 10-12 years of age and aseptic meningitis commonly occurs after 2 years of age **[Table 1].** Out of fifty-seven cases (n=57) of bacterial meningitis, twenty-two cases were culture negative and thirty-five cases were culture positive. Twenty-two cases (22,62.8%) out of thirty-five cases were streptococcus pneumonia followed by eight cases (8,22.8%) were Neisseria meningitis, Haemophilus influenza found in three cases (3,8.5%), *E.coli* found in two cases (2,5.7%) **[Table 2].** WBC count & PMN (%) were increased significantly in bacterial meningitis, mean of 5021. Protein and glucose

levels in CSF were not significantly different between bacterial meningitis and aseptic meningitis **[Table 3].** In the case of bacterial meningitis, in fifty-one cases (51,89.4%) out of fifty-seven, the CSF CRP test was truly positive, with mean±SD 21.7±10.9, false negative were only six cases (6, 10.5%). In aseptic meningitis thirty-nine cases (39,90.6%) out of forty-three cases, the CSF-CRP test was truly negative, and false positive were four cases (4,9.3%) [**Table 4].** The sensitivity of CSF CRP in differentiating bacterial meningitis from aseptic meningitis was 89.47%, specificity 90.69%, & diagnostic accuracy 90% **[Figure 1].**

Table 1: Distribution of the study population based on characteristics (N=100)

Characteristics	**(N,%)**
Age	
0-2 years	43, 43.0%
3-6 years	27, 27.0%
7-9 years	19, 19. .0%
10-12 years	11, 11.0%
Sex	
Male	60, 60.0%
Female	40, 40.0%
Types of meningitis according to age	
Bacterial meningitis	
0-2 years	35, 35.0%
3-6 years	11, 11.0%
7-9 years	7, 7 .0%
10-12 years	4,4.0%
Aseptic meningitis	
0-2 years	6, 6.0%
3-6 years	16, 16.0%
7-9 years	12, 12.0%
9-12 years	9, 9.0%

Table 2: Distribution of the study population based on Bivariate aetiopathogenesis of Bacterial meningitis 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	10,45.4%	5,62.5%	1,33.3%	1,50.0%
H. influenzae	6,27.2%	00	00	00
N. meningitidis	4,18.1%	3,37.5%	2,66.6%	1,50.0%
E. coli	2,9.0%	00	00	00
Organism not found (n=22)	-	-	-	-
Total=57	**22**	**08**	**03**	**02**

Table 3: Distribution of the study population based on Laboratory characteristics of CSF (N=100)

Parameters	**Bacterial meningitis (n=57)**	**Aseptic Meningitis (n=43)**	***P value***
Total WBC (mm3)	(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 4: Distribution of the study population based on CSF C - reactive protein test results ((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	39	2.1±1.2 06	
CRP Negative	06		04		
Total	**57**		**43**		

*P value from ANOVA test calculator

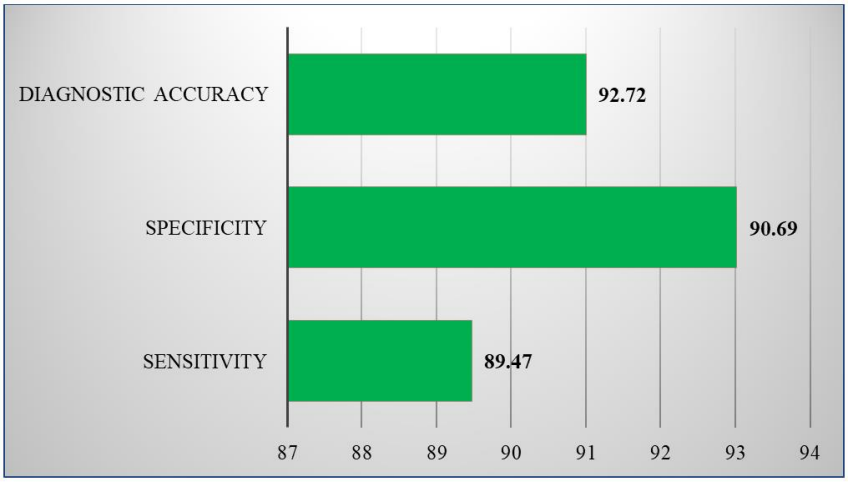

Figure 1: Figure showing Sensitivity, Specificity, & Diagnostic accuracy of the CSF-CRP test result

DISCUSSION

Bacterial meningitis is life-threatening and more common in children under one year of age to sixteen years of age. Increased awareness and initial recognition and appropriate antibiotic treatment can decrease morbidity and mortality. In a developing country, conveniences to suitably isolate blood- or CSF-borne organisms are limited, and if available culture reports are time-consuming. CSF-CRP is a test that meets all criteria and unlike CSF cytology and biochemistry does not require acquaintance to interpret the results. In this current study, most of the patients (43,43.0%) were 0-2 years of age. Bacterial meningitis 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, 9% at 10-12 years). Most of the organisms 22 cases (62.85%) were streptococcus pneumonia followed by 08 cases (22.85%) were Neisseria meningitis, Haemophylusinfleunza 3 cases (8.57%), *E.coli* were 02 cases (5.71%). Similar observations were also reported in another article where streptococcus pneumonia was the most common organism (66.7%) followed by Neisseria meningitis, Haemophilus influenza, and *E.coli* [15]. In the present study, CSF-CRP was positive in 51 (89.47%) cases of Bacterial meningitis, and 3 (6.97%) cases of aseptic meningitis. Another study reported that 84% of their cases of pyogenic meningitis had a positive CSF-CRP [13]. A study suggested a statistically significant higher level of CRP in CSF of the patient with bacterial meningitis in contrast with aseptic meningitis [13]. However, another study reported that only 35% of bacterial meningitis cases are CSF-CRP positive [15]. The present study reported the CSF-CRP to have a Sensitivity, Specificity, and Diagnostic Accuracy (DA) of 89.47%, 90.69%, 92.72%, 86.66%, and 90% respectively. Another article concluded that CSF-CRP had a sensitivity of 84%, a specificity of 100%, and a positive predictive value of 100% [16]. CRP migration to CSF is not properly explained in the literature. CSF-CRP levels were found to be lower than that of serum CRP. This difference was explained by the direct hepatic release of CRP into plasma which then undergoes ultrafiltration to form CSF [17]. 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 [18]. Only 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 another finding [15]. 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 [15]. In multiple findings, CSF-CRP was positive in 66% and 85% were cut-off values for positive were at the level of >1mg/L and >0.5mg/L respectively [19, 20]. 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 [15, 21]. 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, with a sensitivity of 89.47% and specificity of 90.69%.

CONCLUSION

Meningitis is an acute inflammation of the membranes layering the brain and spinal cord. The

kinds of meningitis from CRP levels in CSF offer high sensitivity and moderate specificity. It is an easy, precise technique for laboratory diagnosis and is particularly suitable for bacterial meningitis. Diagnostic accuracy can be applied as the initial test for the diagnosis of bacterial meningitis.

RECOMMENDATIONS

The negative parameters are not a rationale for the exclusion of the diagnosis of bacterial meningitis and it would be hard to justify not treating patients in the first hours of diagnosis with antibiotics or to suggest a nonbacterial etiology. Further studies are needed to reach this conclusion. Furthermore, a multicenter study should be conducted with a large sample size to know the pathophysiology of CSF-CRP and the diagnostic accuracy of the test for differentiating between bacterial and aseptic meningitis.

FUNDING

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CONFLICT OF INTEREST

None declared.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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