Original Article

Childhood Bacterial Meningitis and Usefulness of C-reactive Protein

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Abstract

Background : C-reactive protein raises rapidly in the first 24-48 hours of occurrence of bacterial meningitis and in large incremental increases thereafter. This prospective study was undertaken in a tertiary care hospital of Armed Forces to ascertain the usefulness of C-reactive protein in early diagnosis of bacterial meningitis.

Methods : All children admitted during the period of study, with clinical suspicion of meningitis were clinically, biochemically, cytologically and bacteriologically investigated to clinch the diagnosis. Blood and CSF were also sent for C-reactive protein assay by latex agglutination test. CSF gram staining, culture and biochemical results were taken as gold standard. CSF and serum CRP were then evaluated against this gold standard. Statistical analysis was done by Epiinfo 6.

Results : There were 63 cases of meningitis admitted in the hospital. By gold standard, there were 38 cases of bacterial, 21 cases of tubercular and 4 cases of viral meningitis. H. influenza was the predominant organism grown. CSF C-reactive protein was raised in 33 cases of bacterial and 2 cases of tubercular meningitis. Serum C-reactive protein was raised in 29 cases of bacterial, and eight cases of tubercular meningitis. These tests were negative in all cases of viral meningitis. The sensitivity and specificity of serum and CSF C-reactive protein was 96% and 100%.

Conclusion : Quantitative and qualitative assay of C-reactive protein is a simple bedside test. It can be completed in 10 minutes and requires only 0.2 ml of blood. This will significantly reduce unnecessary antibiotics to children.

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Key Words : C-reactive protein; Meningitis; Children

Introduction

Bacterial meningitis is a significant cause of mortality and morbidity in children worldwide. Neurological outcome and survival depend largely on damage to central nervous system prior to effective antibacterial treatment. Quick diagnosis and effective treatment is the key to success. The diagnostic dilemma in acute bacterial meningitis is due to large spectrum of signs and symptoms. However, it is usual practice to start antibiotics before the complete laboratory result is available. Such blind prescriptions are usually in nonmeningitic doses. Majority of children who report to hospital, therefore, have already been treated with inadequate doses of antibiotics and present atypical features in cerebrospinal fluid examination (CSF) [1].

Various hematological indices have been initiated to screen for bacterial meningitis, majority being neither highly sensitive nor specific. C-reactive protein (C-RP), an acute phase reactant, has been used to diagnose and follow the course of infection[2]. Its advantages include its very low serum levels in normal infants and children, a rapid rise within 12 to 24 hours of infection and a large incremental increase thereafter. The present study was undertaken to establish the utility of C-RP in both serum and CSF in early diagnosis of bacterial meningitis in children.

Material and Methods

63 pediatric patients clinically suspected and confirmed by gold standard of having meningitis were included in the study. The study was undertaken in a tertiary care hospital. At the time of admission, relevant history regarding clinical symptoms and signs, details of treatment (antibiotics) taken prior to admission and duration of illness was recorded.

After admission, all children (1 month to 12 years) included in the study were subjected to routine hematological investigations like Hb%, total leukocyte count, differential leukocyte count, peripheral blood smear, blood glucose, X-ray chest, blood culture, cytological, biochemical, Gram staining and culture of CSF and C-RPstudy of CSF. Blood was also collected for serum C-RP. The "gold standard" for the diagnosis of bacterial meningitis was predominant polymorphonuclear cells > 1000 cells/mm^3, raised protein > 400 mg/dl, ratio of CSF and blood glucose < 40%, positive gram staining and / or positive CSF culture for bacterial pathogen. The diagnosis of tubercular and viral meningitis was considered on characteristic CSF cells, protein, glucose level and Gram staining and culture report [3].

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Bacteriological studies on the CSF were performed in the Department of Microbiology. Each specimen was centrifuged at 1000 rpm for 5 minutes. The supernatant was removed aseptically into a separate tube and used for bacteriological antigens. The sediment was cultured using standard technique and also used for Gram staining. All colonies were identified on the basis of their colony morphology and culture characteristics and their biochemical reactions according to standard procedures.

Method of C-RP estimation

C-RP was detected by latex agglutination method using commercial kit "Immunoscreen-CRP" by Monozyme. The test utilizes uniform latex particles coated with anti human C-RP which show agglutination in presence of C-RP. The qualitative test was performed on the clinical samples by mixing a drop (40 µL) of specimen with 25 µL of latex reagent on a disposable slide. Both were mixed gently. The test was considered positive if clear agglutination was visible within 2 minutes. Absence of agglutination within 2 minutes indicated negative sample. A positive and negative control was also run in parallel with each test. The sensitivity of the test was 6mg/L or more. Statistical analysis was performed using the Epi info 6.

Results

There were 38 cases of bacterial meningitis, 21 cases of tubercular meningitis and 4 cases of viral meningitis based on biochemical, cytological, Gram staining and positive culture report of CSF (Table 1). CSF culture was positive only in 3 cases of bacterial meningitis and Gram staining was positive in 8 cases of bacterial meningitis. *H influenza* was the agent identified in 2 cases and *S pneumoniae* in one case. *H influenza* was seen in < 1-year-old child.

Table 1

Diagnosis of cases based on CSF study

Disease	No	%
Bacterial meningitis	38	60.3
Tubercular meningitis	21	33.3
Viral meningitis	04	6.4

Raised C-RP in CSF was found in 33 cases of bacterial meningitis, 2 cases of tubercular meningitis and no case of viral meningitis. Serum C-RP was found raised and positive in 29 cases of bacterial meningitis, 8 cases of tubercular meningitis and no case of viral meningitis (Table 2).

Out of 38 cases of bacterial meningitis, prior antibiotics were used for 7days or less in 12 cases. These cases also showed low-grade CSF pleocytosis and negative Gram stain. Serum C-RP and C-RP in CSF was found negative in 9 and 5 cases of bacterial meningitis respectively and all 4 cases of viral meningitis. C-RP in serum and CSF was not found positive in any case of viral meningitis. Serum C-RP and C-RP in CSF was found raised in 8 and 2 cases of tubercular meningitis respectively.

Raised level of C-RP in CSF was found sensitive in 86.6% and specific in 92% cases. Serum C-RP had sensitivity of 76% and specificity of 68%. Raised level of C-RP in CSF and serum C-RP combined were found sensitive in 96% and specific in 100% cases. Positive value of raised C-RP in CSF alone was 94% and in combination with raised serum C-RP was 100%. Negative predictive value of raised C-RP in CSF alone was 82% and in combination with serum C-RP was 93%.

Table 2

Comparison of various investigations

Disease	No	Serum +ve	CRP -ve	CSF +ve	CRP -ve	Gram stain +ve	-ve	CSF culture +ve	-ve
Bacterial meningitis	38	29	09	33	05	08	30	03	35
Tubercular meningitis	21	08	13	02	19	00	21	00	21
Viral meningitis	04	00	04	00	04	00	04	00	04

Discussion

In our evaluation of utility of C-RP assay, the diagnosis of bacterial meningitis was based on positive culture of CSF, identification of organism in Gram stain and / or characteristic CSF cytological and biochemical parameter. C-RP evaluation thus helped in diagnosing 11(17.5%) cases of bacterial meningitis. CSF culture report was, however, available after more than 72 hours.

Tatara R found raised level of serum C-RP the most useful test for differentiating between bacterial and aseptic meningitis[4]. We found serum C-RP sensitive in 76% and its specificity was 68%. However, its diagnostic accuracy in comparison with other lab parameters is yet to be evaluated.

Raised level of C-RP in CSF was found to be a better marker than serum C-RP. Similar view has been expressed by other workers who found raised level of C-RP in CSF a better indicator of bacterial meningitis (sensitivity 91%). It also served to distinguish bacterial from viral, tubercular or other central nervous system disorders [5]. Abraham et al also found that raised level of C-RP in CSF was able to detect bacterial meningitis with a sensitivity of 97% and specificity of 86% [6]. Corrall CJ found C-RP in CSF had a sensitivity of 100% and specificity of 94%. It was a more sensitive test for differentiating bacterial from non bacterial meningitis than any other lab test on CSF [7].

Predictive accuracy of a test provides greater practical value. Negative predictive value of raised C-RP in CSF alone was 82%. However, other workers have reported a negative predictive value of 95-100%[6,8]. Positive predictive value of raised C-RP in CSF and serum C-RP was 94% and 78% respectively.

Serum C-RP and C-RP in CSF test results were

combined together and combined test had sensitivity of 96% and specificity of 100%. Negative predictive value of combined results of serum C-RP and C-RP in CSF was 93% and positive value was 100%. Raised level of C-RP in CSF is more significant than raised CRP in serum [9]. Positive predictive value and negative predictive value are influenced by size of sample and prevalence. Hence likelihood ratio was calculated which was found to be 0.96 for combined serum and C-RP in CSF. Thus, we found that utility of raised level of C-RP in CSF in combination with raised level of serum C-RP increases sensitivity and specificity of the test and negative tests definitely rule out the diagnosis of bacterial meningitis.

Qualitative assay of C-RP is simple to perform at the bedside be medical staff. It is readily completed within 10 minutes, utilizing only 0.2 ml of infant's blood. Sound clinical judgement combined with qualitative C-RP assay should provide a rational basis for treatment decision in the management of bacterial meningitis. This will significantly reduce unnecessary antimicrobial therapy, ensure adequate dosage of antibiotics and will also prevent emergence of resistant strain of microorganisms.

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