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Detection of C-Reactive Protein in Cerebrospinal Fluid for Rapid Diagnosis and its Role in Differentiation of Meningitis

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Abstract
Background: *Pyogenic meningitis is a devastating infection of the central nervous system that has a high mortality and morbidity in spite of the availability of several new potent antimicrobials. It requires rapid and correct diagnosis to select appropriate therapy.*
Objective: *Detection of C-reactive protein in CSF and assessment of the diagnostic performance of it in differentiation of meningitis.*
Methodology: *It is a prospective study of cases comprising of suspected CNS infections in children from the community over a specific period of time. C-reactive protein titre in CSF of 132 cases of infants and children (0-16yrs) were detected using semiquantitative latex agglutination method.*
Results: *Of total 132 cases studied, 44 cases were pyogenic meningitis (33.33%), 14 cases were tuberculous meningitis (10.61%), 48 cases were viral encephalitis (36.36%), and 26 were with extra cranial infections (19.70%). CSF CRP was positive in 43 out of 44 cases of pyogenic meningitis with 97.73% sensitivity, and 97.73% positive predictive values.*
Conclusion: *Detection of CRP in CSF and serum provides a new dimension to specific diagnosis of pyogenic meningitis and differentiation from other CNS infections. It is a sensitive, reliable, early diagnostic test for timely therapeutic intervention. From this study it is concluded that a positive CSF CRP detected by latex agglutination method may be considered to have pyogenic meningitis and treated likewise until proved otherwise.*
Keywords*: Cerebrospinal fluid, C-reactive protein, Latex agglutination, Pyogenic meningitis*

I. Introduction

The central nervous system (CNS) is particularly susceptible to infection during the period of maximum growth, from foetal life to early childhood. Regardless of aetiology, most patients with CNS infection have similar clinical manifestations. The severity and constellation of signs are determined by the specific pathogen, the host, and the area of the CNS affected.[1] The goal is to begin antibiotic therapy within 60 minutes of a patient's arrival in the emergency room. Empirical antimicrobial therapy is initiated in suspected patients before the results of CSF Gram's stain and culture are known.[2] Delay in distinguishing bacterial from other infections of central nervous system may have irrevocable consequence, as the regenerative capacity of central nervous tissue is limited, so prompt and correct diagnosis to select appropriate therapy is required.[3] CRP in CSF has been reputed to be one of the most reliable and early indices for differentiating bacterial from non-bacterial meningitis. Many workers have found CSF and serum CRP test as a reliable and specific bedside test in the early diagnosis of meningitis.[4] It is also useful in monitoring the clinical course of the disease.[5] Many workers have found serum and CSF CRP test as an early diagnostic test in differentiating bacterial from non-bacterial meningitis, and a reliable test for timely therapeutic intervention.[6,7-10] The present study was undertaken to evaluate the use of cerebrospinal fluid (CSF) C-reactive protein (CRP) in the rapid diagnosis of pyogenic meningitis and differentiation from other infections of central nervous system (CNS).

II. Methodology

The study was conducted in the Department of Pediatrics and Neonatology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand. Infants and children between 0-16 years admitted with suspicion of meningitis during the period from Jun 2014 to May 2015 were included in the study group.

Detailed history and thorough examination were done in each case and a tentative diagnosis was made. Blood and CSF samples were collected as a part of diagnostic work up. CSF specimen was collected by lumbar puncture under aseptic precautions for routine CSF examination-cell type and count, protein and sugar. Blood was collected for hemogram and culture. Depending upon the CSF analysis cases were divided into 4 groups: Group I-Pyogenic meningitis, Group II-Tuberculous meningitis, Group III-Viral encephalitis and Group IV-Extra cranial infections. A semi quantitative latex agglutination test was done to determine the level of CRP in CSF. Here, using diluted glycine saline buffer, serial dilutions of serum samples were prepared from 1:2 to 1:64.

To each of this sample CRP-latex reagent was added as before and agglutination watched for. Agglutination in right serum sample or dilution corresponds to the approximate amount of CRP in the specimen.
The concentration of CRP was then calculated as follows: CRP (mg/dl) = 6 × D
Where D is the highest dilution of serum agglutination observed Diagnostic performance of CRP was assessed by using the Sensitivity, Specificity, PPV, NPV and Accuracy.

III. Results

132 patients who met the inclusion criteria with 44 cases of Pyogenic Meningitis (Group I), 14 cases of Tuberculous Meningitis (Group II), 48 cases of Viral encephalitis (Group III) and 26 without CNS infections (Group IV) were undertaken to study the use of C-Reactive Protein in the rapid diagnosis and differentiation of Pyogenic meningitis from other infection of CNS.

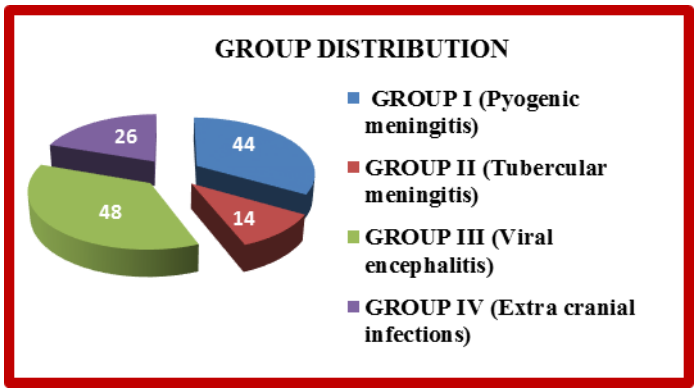

Fig: Group Distribution (n=132)

Table 1: Comparison of serum and CSF CRP in various groups

	GROUP I		GROUP II		GROUP III		GROUP IV	
NUMBER OF CASES	n=44		n=14		n=48		n=46	
TEST	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
SERUM CRP	43 (97.73%)	1(2.27%)	14 (100%)	0	6 (12.5%)	42 (87.5%)	0	26 (100%)
CSF CRP CUTOFF VALUE ≥ 12 mg/dl	43 (97.73%)	1(2.27%)	1(7.14%)	13 (92.86%)	0	48 (100%)	0	26 (100%)
TOTAL	44		14		48		26	

In chronic inflammation serum CRP can be positive thus explaining the positivity of serum CRP in GROUP-II. Thus in such cases a serial serum CRP estimation would be helpful. The positivity rate of serum CRP in Group I was 97.73%, Group II was 100%, Group III and IV insignificant. The positivity rate of CSF CRP was 97.73% in Group-I, 7.14% in Group II and nil in others. The serum CRP was unable to differentiate between Group I and II because of 97.73% sensitivity, 0% specificity with 75.44% positive and 0% negative predictive values. The CSF CRP was able to differentiate between Group I and Group II with 97.73% sensitivity, 92.86% specificity with 97.73% positive and 92.86% negative predictive value.

IV. Discussions

Table1 shows CSF CRP being 97.73% positive with significant p value (p=0.001) in GROUP I, here the cut off of CRP was taken as 12mg/dl. GROUP-II had 2 cases positive with 1 having 12mg/dl, and the other, less than the cut off value. In other group the CRP titre was less than 6 mg/dl. In a similar study done by Gaur A, Seshan SV[11] CSF CRP was positive in 80% cases of pyogenic meningitis, 24 of 30 cases, here CRP cut off

was taken as 12mg/dl, as the kit could detect this as minimum concentration. In another similar study done by Gokul BN et al[12] CSF CRP was positive in 84% cases of pyogenic meningitis, that's 37 of 44 cases. In a study done by John M et al[13] CSF CRP was positive in 100% cases of pyogenic meningitis and virtually negative in tuberculous meningitis.

Table 2 showed that positivity rate of serum CRP in Group I was 97.73%, Group II was 100%, Group III and IV insignificant. The positivity rate of CSF CRP was 97.73% in Group-I, 7.14% in Group II and insignificant in others. The serum CRP was unable to differentiate between Group I and II because of 97.73% sensitivity, 0% specificity with 75.44% positive and 0% negative predictive values. The CRP in CSF was able to differentiate between pyogenic meningitis and viral encephalitis with 97.73% sensitivity, 100% specificity and 100% positive and 97.96% negative predictive value.

In the study by Gaur A et al[11] CSF CRP had 80% sensitivity, 100%specificity, 100% positive and negative predictive value. The study done by Pemde HK et al[14] showed CSF CRP was positive in all cases of pyogenic meningitis, and CSF CRP could differentiate pyogenic meningitis from tuberculous with 100% sensitivity, 95% specificity, 100% negative predictive value. All corresponding values were 100% when CSF CRP was used to differentiate pyogenic meningitis from no meningitis group. In study done by Gokul BN et al[12], CSF CRP detected by latex agglutination had 84% sensitivity, 100% specificity. High values of sensitivity (100%), specificity (95-100%), positive and negative predictive value (100%) have been noted in many studies[10,12,15] as shown in Table 3 with CSF CRP being a very useful tool in differentiating various meningitic groups.

Table 2: Comparison of CSF CRP among different studies

GROUPS	PRESENT STUDY	GAUR A et Al[100]	B.N GOKUL Et al[94]	H.K.PEMDE et al[4]
PYOGENIC MENINGITIS	(n=44,43+ve CRP) 97.73%	(n=30,24+ve CRP) 80%	(n=44,37+ve CRP) 84%	(n=30,30+ve CRP) 100%
TUBERCULOUS MENINIGITIS	(n=14,1+ve CRP) 7.14%	(n=40,6+ve CRP) 15%	(n=57,nil+ve CRP) 0%	(n=40,2+ve CRP) 5%
NO MENINGITIS	(n=74,0+ve CRP) 0%	(n=30,nil+ve CRP) 0%	(n=109,nil+ve CRP) 0%	(n=30,nil+ve CRP) 0%

Table 3: Diagnostic values of CSF CRP among different studies

(Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), of CSF CRP Test between Pyogenic Meningitis and Tuberculous Meningitis)

STUDIES	**SENSITIVTY**	**SPECIFICITY**	**POSITIVE PREDICTIVE VALUE (PPV)**	**NEGATIVE PREDICTIVE VALUE (NPV)**
PRESENT STUDY	97.73%	92.86%	97.73%	92.86%
GAUR A et al	80%	100%	100%	100%
PEMDE HK et al	100%	95-100%	100%	94-100%
GOKUL BN et al	84%	100%	-	-

V. Conclusion

Detection of C-reactive protein in CSF and serum appear to provide a concrete dimension to specific diagnosis of pyogenic meningitis and differentiation from other CNS infections. It is an easy, quick to perform, sensitive, reliable and rapid diagnostic test for timely therapeutic intervention. The detection of CRP in CSF also helps in the choice of appropriate antibiotic and the duration of therapy. From this study it is concluded that a quantitative positive CSF CRP (>12mg/dl) detected by latex agglutination method may be considered as pyogenic meningitis and treated likewise.

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