

## CEREBROSPINAL FLUID C-REACTIVE PROTEIN IN THE DIAGNOSIS OF MENINGITIS IN CHILDREN

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### ABSTRACT

*C-reactive protein was evaluated in the cerebrospinal fluid of 250 patients to determine if its measurement is of any clinical value in the diagnosis of bacterial meningitis. The C-reactive protein was found to be significant in the diagnosis of bacterial meningitis.*

**Key words:** *C-reactive protein, Cerebrospinal fluid, Bacterial meningitis, Aseptic meningitis.*

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*Received for publication: March 22, 1993;*

*Accepted: March 22, 1994*

There has been recent resurgence of interest in the diagnostic use of C-reactive protein (CRP) in clinical medicine(1-7). The rediscovery of this acute phase reactant is largely the result of improved, rapid, accurate, qualitative methods of measurement that can be performed easily by most clinical laboratories. Occasionally, there is difficulty in distinguishing bacterial meningitis (BM) from aseptic meningitis (AM) on the basis of commonly used laboratory tests. A number of recent studies strongly suggested that measurements of CRP in cerebrospinal fluid (CSF) could reliably discriminate between them, implicitly recommending their routine clinical application. A prospective study was, therefore, designed to evaluate the relative predictive value of CRP against standard CSF laboratory determinations for distinguishing BM from AM.

### Material and Methods

CSF specimens were obtained from 250 patients admitted to the pediatric ward of Patna Medical College from February 1986 to October 1987. The patients age ranged from one week to 18 years. They were grouped as follows:

(a) One hundred and thirty cases of BM: Only culture proven cases were included in this group. The organisms isolated were *Hemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis*.

(b) Seventy patients of AM: Only those cases were included in this group which had characteristic symptoms and signs of meningitis and had not received any antibiotic prior to admission and their CSF white cell count were more than 10 cells/mm<sup>3</sup> but less than 1000 cells/mm<sup>3</sup> with lymphocytic predominance (more than 60%), glucose exceeded 45 mg/dl with marginal rise of protein and negative Gram

staining. The CSF and blood culture in all these patients were negative. They were assumed to be cases of AM and were treated on the lines of AM with excellent recovery. The specific etiology of AM could not be determined.

(c) Fifty patients with no meningitis: These were cases with the first attack of febrile convulsion or acute febrile illness in whom meningitis was suspected. CSF showed no pleocytosis and glucose and proteins were within normal range. They served as control group.

CRP was tested by latex agglutination method, without dilution of the CSF. Specimens were kept in sterile pyrogen free tubes at 4°C and were tested within 12 hours. Routine CSF analysis included Gram stain, bacteriologic cultures, total and differential cell counts, protein and glucose quantitation.

## Results

The positive cases of CSF-CRP in different groups are summarized in *Table I*.

In the BM group the diagnosis was possible in 73 patients, prior to culture report on the basis of CSF cytology, protein, glucose, estimation and Gram staining. The CRP in CSF was positive in 70 out of 73 patients. In the remaining 57 patients, diagnosis was not established before culture report because there was minimal elevation of CSF protein and cells count and Gram staining were negative. In all of these patients except one, the CRP was positive. They were the partially treated cases of BM and had been given antibiotic prior to admission.

In all the patients of AM and no meningitis group, CSF-CRP was negative. Thus according to the results of CSF-CRP, the sensitivity was 96.9%, specificity 100%, predictive value of positive test 100% and predictive value of negative test 96.7% for BM.

## Discussion

Even after 50 years of its discovery, the precise nature of the CRP is still uncertain. CRP was first detected in pneumonia by

**TABLE I**-Cerebrospinal Fluid. CRP Measurement and CSF Total Protein, Number of Neutrophils and Gram Staining in Different Groups

Group	No. of patients	Positive CRP	CSF		
			Positive Gram staining	More than 50 neutrophils	Elevated protein
(a) Bacterial meningitis					
(i) Diagnosis Possible prior to culture report	73	70	58	65	66
(ii) Diagnosis not possible prior to culture report	57	56	0	9	8
(b) Aseptic meningitis	70	0	0	14	16
(c) No meningitis	50	0	0	0	3

Tillet and Francis(8). Also known as acute phase protein, it is an abnormal globulin which appears in the serum of patients suffering from inflammatory conditions of infectious or non-infectious origin. It is absent from the serum of healthy individuals. It appears within hours of tissue damage and disappears with the same rapidity after the cessation of the destructive process. The site of origin, fate or function of this globulin is not definitely known.

With the advent of more sensitive and precise assays for the measurement of CRP levels there has been a recent resurgence of interest in its biological applications(4). The analysis of CSF-CRP by latex agglutination is rapid and is easy to perform. There are varied reports about the sensitivity of CSF-CRP in predicting BM. Corral *et al.*(9) found that CRP was elevated in the CSF of all the 24 patients with culture proven BM but in only two of 32 patients with non-bacterial meningitis. Walterpiel(10), later noted that CSF specimens from four of 10 children with *H. influenzae* meningitis were negative by the latex agglutination test for CRP. The CSF from neonates with BM was tested for CRP by Phillip and Baker(11) using a sensitive Laser Nephelometry technique, they found elevated CRP levels in only two of 11 patients with culture proved BM. Benjamin *et al.*(12) also reported a low sensitivity (66%) when Laser Nephelometry was used to detect CRP in the CSF of patients with BM. Abramson *et al.*(13) found that in 72 of 74 patients with BM, CRP was detectable by latex agglutination assay. Elden *et al.*(14) reported that 14 (82%) of 18 patients with BM had detectable CRP in CSF.

In our study, 126 of 130 patients of BM showed positive CRP in the CSF. Out of 4 patients with negative results, 3 were neo-

nates in which negative results might be due to prozone phenomenon. A number of factors (*e.g.*, specimen handling, age of the patients, underlying disease) might explain the divergent results reported for the sensitivity of the CRP assay. Our study and three others(9,13,14) reported the highest sensitivity with use of the latex agglutination assay.

Using CSF pleocytosis and raised protein as the sole criteria for beginning of antibiotic therapy in the patients, in this study at least 21 patients would have received antibiotic therapy, although they were actually cases of AM (as proved by follow up without antibiotic therapy). If we would have decided to treat only when an abnormality was detected in Gram stain or CSF culture, then there would have been high mortality in 57 patients.

BM is a potentially devastating illness that\* requires prompt recognition and early appropriate therapy. There is certainly no value in performing the test if Gram stain of the CSF demonstrate organism. In about 80% of cases of BM, the Gram stain was positive. The problem was with the remaining 20% of cases and subjects who had been given prior antibiotics. The value of CRP lies in the management of these Gram stain negative patients in whom delay, in the specific treatment, till the culture report were available will be devastating.

The present study suggests that a patient with any degree of CSF pleocytosis and raised protein level who has a positive CRP in the CSF should be treated for presumed BM. Patients with low grade pleocytosis (less than 50 neutrophils/cm) who have normal CSF glucose and protein and a negative Gram stain and in whom the clinical picture is very suggestive of a viral etiology, the absence of CRP in the CSF may be an

additional piece of information that will assist the clinician in withholding antibiotic therapy. While closely observing the patients, where any doubt exists it is recommended that the patient should be treated as a case of BM until culture results are available.

Our observations suggest that the routine use of CSF-CRP may be useful and patients with positive CRP in the CSF should be treated presumptively for bacterial meningitis. Thus, easily performed rapid CRP determinations can considerably improve the quality of care in meningitis patients, especially in those situations where facilities for performing bacterial cultures of antibiotic susceptibility testing are not available and it can even be used as a bedside test in the rapid diagnosis of bacterial meningitis(15).

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