

C-REACTIVE PROTEIN AS AN INDICATOR OF COMPLICATIONS IN BACTERIAL MENINGITIS

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Objective: To determine the value of serum C-reactive protein (CRP) estimation in the follow-up of bacterial meningitis (BM). **Design:** Longitudinal follow-up. **Setting:** Urban hospital. **Methods:** Sequential serum CRP estimation was done in 50 healthy children and in 100 children with BM. Serial serum CRP value was correlated with the clinical picture in BM. **Results:** Serial serum CRP in 14 patients with complicated BM was significantly different than the 72 uncomplicated BM cases. **Conclusions:** Serial determination of serum CRP may be a cheap, simple and reliable prognostic indicator in BM.

Key words: Bacterial meningitis, C-reactive protein.

SINCE the first report on the utility of C-reactive protein (CRP) in the diagnosis of bacterial meningitis (BM)(1), several studies have confirmed that determination of CRP in cerebrospinal fluid (CSF) or serum is of great value in the differential diagnosis of BM(2-4). Besides differential diagnosis, sequential determination of CRP is of great value in monitoring the course of illness (5-7). The present study was designed to evaluate the reliability of serial serum CRP measurement in the follow-up of BM.

Subjects and Methods

One hundred untreated children (55 males and 45 females) aged between 2 weeks to 12 years with bacteriologically confirmed BM were included in the study which continued from October 1990 to July 1994. BM was diagnosed by the characteristic symptoms, signs and CSF picture with a positive CSF culture. Serum CRP levels were estimated by a modified latex particle agglutination technique using a kit (Rapi-Tax CRP Hoechst

Pharmaceuticals Ltd., Bombay).

Serum CRP estimation was done on the first day when the patient presented to us and then on every third day. On the average five CRP estimations were performed; during the course of treatment except in 14 cases who showed clinical signs of complications like sub-dural collection, hydrocephalus, prolonged fever, convulsions, irritability *etc.* In these cases CRP was measured once in 24 hours once the complications were detected clinically and CSF examination, ultrasonography (infants with open fontanelles) and CT scan of skull were also done. Sera from 50 randomly chosen healthy children of the same age group were serially tested at one week interval for 2 weeks in the control group. Values thus obtained were utilized to determine a single mean value for the CRP. Apart from BM, other causes resulting in raised CRP were ruled out in all the patients. All patients of BM were treated with penicillin, chloramphenicol, cefotaxime and ceftriaxone

in various combinations based on the clinical improvement and sensitivity report.

The cut off point for elevated serum CRP level was taken as 10 mg/L, and slow decrease of CRP was called when decreased serum CRP level remained above 30 mg/L after 5 to 6 days of therapy or it did not fall below 10 mg/L even after 10 days of therapy, a slow decrease of CRP was defined.

Results

The organisms isolated were *Haemophilus influenzae* (n=39), *Streptococcus pneumoniae* (n=31), *Neisseria meningitidis* (n=18), *Staphylococcus aureus* (n=4), [3-hemolytic *Streptococcus* (n=3), *Escherichia coli* (n=4) and *Klebsiella pneumoniae* (n=1). Fourteen patients were excluded from the study either due to death early in the course of illness (n=9) or they went to some

other hospital (n=5).

The mean value of CRP in the control group was 3.06 mg/L (SD±1.27). In 72 patients of the study group there was uneventful recovery and the first mean CRP level was 22 mg/L. (SD ± 3.99; range 14-30 mg/L). The CRP levels peaked on 3rd day (30 mg/L; SD ± 4.36; range 24-41 mg/L) and normalized (6 mg/L) within 10 days. In the remaining 14 patients with complications, CRP levels changes are summarized in *Table I & Fig. 1*. There was a significant difference in the serial serum CRP levels (p <0.01) between the complicated and uncomplicated BM from the fourth day onwards.

Five patients showed recovery till day 5 or 6 when they developed persistent cry or vomiting. The CRP estimation at this stage revealed a progressive rise (peak mean CRP level 51.6 mg/L). Out of these 3 had hydrocephalus and 2 subdural effusion

TABLE I—CRP Trend in Complicated Bacterial Meningitis

| Case No. | Complication | Etiology | Initial CRP level | CRP Trend | Day | CRP (mg/L) |
|----------|---|----------|-------------------|--------------------|-------|------------|
| 1. | Hydrocephalus | Hi | 18 | Secondary increase | 5-7 | 14-52 |
| 2. | Subdural effusion | Pnc | 28 | Secondary increase | 5-7 | 23-56 |
| 3. | FC, DIC | Hi + Pse | 19 | Secondary increase | 11-14 | 5-110 |
| 4. | Hemiplegia | Hi | 22 | Secondary increase | 5-7 | 26-54 |
| 5. | Persistent high fever | GBS | 20 | Slow decrease | 3-15 | 32-10 |
| 6. | Hydrocephalus | Hi | 23 | Secondary increase | 5-9 | 18-49 |
| 7. | Persistent seizures | Hi | 23 | Slow decrease | 3-13 | 34-8 |
| 8. | Persistent seizures | Hi | 17 | Slow decrease | 3-13 | 31-9 |
| 9. | Subdural effusion | Hi | 16 | Secondary increase | 5-7 | 14-53 |
| 10. | Persistent seizures | Pnc | 26 | Slow decrease | 3-15 | 36-8 |
| 11. | Persistent high fever | Kle | 21 | Slow decrease | 3-21 | 38-7 |
| 12. | Hydrocephalus | Hi | 19 | Secondary increase | 5-7 | 17-48 |
| 13. | Hemiplegia with VII cranial nerve palsy | Pnc | 27 | Secondary increase | 3-5 | 29-62 |
| 14. | Persistent high fever | Staph | 24 | Slow decrease | 3-17 | 33-9 |

Abbreviations: Hi-Haemophilus influenzae; Pse-Pseudomonas aeruginosa; Kle-Klebsiella pneumoniae; DIC-Disseminated intravascular coagulation; FC-Focal convulsion; Pnc-Streptococcus pneumoniae; GBS-β-hemolytic Streptococcus; Staph-Staphylococcus aureus.

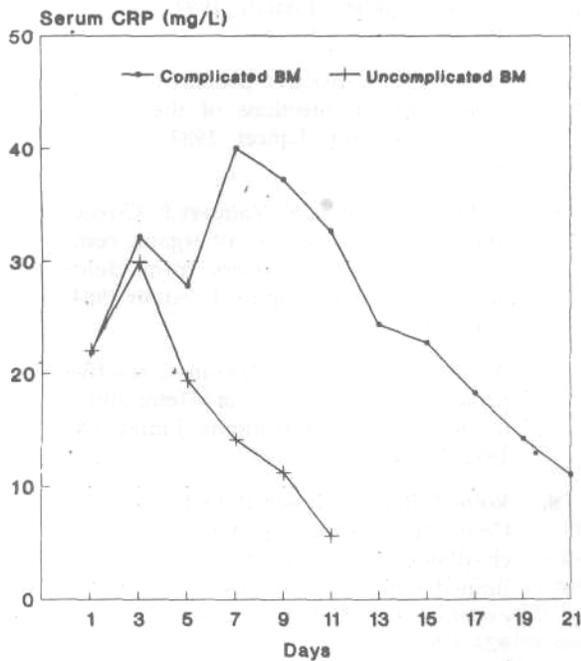


Fig. 1. Graph showing serial mean serum CRP values in uncomplicated BM (n=72) and complicated BM (n=14).

as detected on ultrasound of the skull. With continued antibiotic therapy, 1 patient with hydrocephalus had a continuous fall in CRP level. After 21 days of therapy, the CRP level became normal and the patient fully recovered. In the other 4 patients, CRP levels remained elevated and no improvement occurred till a surgical intervention was done. In 2 patients (1 with hemiplegia and the other with hemiplegia and VII cranial nerve palsy), after an initial decrease, there was a progressive rise of the CRP level from 4th to 5th day. After 21 days of antibiotic therapy, the patients recovered with neurological deficit but the CRP levels remained much above the normal (mean CRP level 25.5 mg/L) till the date of discharge. Follow up after 4 weeks revealed normal serum CRP with partial recovery of hemiplegia in both the patients

while VII cranial nerve palsy recovered completely.

In spite of optimum doses of anticonvulsant therapy, 3 patients had persistent seizures. The CRP levels in the cases showed a slow decrease and remained high till days 10-14 (mean CRP on day 11 was 18 mg/L) when the seizures were controlled. Subsequently, the patients made uneventful recovery, with rapid decrease of CRP level towards normal. Three patients had persistent high fever and their CRP levels decreased slowly. The CRP levels remained high till they became afebrile after 14-21 days of antibiotic therapy. One patient fully recovered with 10 days of therapy and the CRP showed the usual pattern of uncomplicated BM. However, on day 14 when he was to be discharged, there was a sudden clinical deterioration with high fever, convulsions and features of DIC. The child died within 24 hours in spite of all measures (CRP 110 mg/L).

Discussion

As the predictive value of prolonged fever, irritability, vomiting, convulsions or focal signs is negligible, sequential estimation of CRP has been used with encouraging results for monitoring the course of BM(6,8). A similar principle has been applied for acute hematogenous osteomyelitis(9,10). Sequential estimation of CRP does not specifically tell us about the type of impending complication. However, it forewarns about the likelihood of problems in these conditions. In the present study, a slow decrease or a secondary rise followed by slow decrease of serum CRP was suggestive of impending complications and the patients required a change of antibiotics or prolongation of therapy or neuro-surgical intervention. In patients with hemiplegia persistence of raised serum CRP even after recovery from

BM may be due tissue injury(10) secondary to cortical infarction.

The results of this study indicate that serum CRP should be estimated either daily or at least on alternate days in BM. A rise in serum CRP should alert the treating clinician and further investigations can then be planned accordingly. Serum CRP is a simple and readily available test in most of the developing countries. However, further confirmatory evidence is imperative prior to recommending serial serum CRP estimation as a routine in children with bacterial meningitis.

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