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Serum C-reactive protein in early diagnosis of bacterial infections in premature infants

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Serum C-reactive protein (CRP) is known to be produced by full-term infants and children in many diseases causing severe inflammation. We examined the usefulness of CRP as an early indicator of bacterial infection in premature newborn infants. CRP was obtained from 100 patients enrolled in a prospective study. All babies were suspected of having bacterial infection (meningitis-septicaemia) because of complications during pregnancy and/or symptoms suggestive of infection during the perinatal period. CRP was measured with the radial immunodiffusion technique. Examinations were done daily as long as elevated serum CRP levels were found.

100% (6/6) of our patients with culture-proven bacterial infections showed elevated CRP values within 24 h after the first clinical or laboratory signs suggesting sepsis. In 52.3% (11/21) of cases most probably suffering from infection, CRP rose within 72 h after the appearance of other symptoms. Even extremely immature infants were able to react with elevated CRP concentrations. Peak values of CRP were independent of birth weight. On the other hand, only 2.7% (2/73) of babies without findings of infection had slightly elevated amounts of CRP for a short time. Thus, serum CRP levels are a helpful parameter for the early diagnosis of severe bacterial infection in premature infants.

Although a delay in initiating antimicrobial therapy in bacterial sepsis of premature infants may be fatal, convenient and reliable tests which indicate the presence or absence of infection are still rare. For differential diagnosis the clinician uses various but often uncertain methods: clinical symptoms, erythrocyte sedimentation rate, neutrophil count [10], cell morphology, platelet count, levels of serum bilirubin or immunoglobulin M, plasma fibrinogen, fibrin split products, evidence of disseminated intravascular coagulation or the NBT-test. An antibiotic treatment must mostly be started without or before a positive bacterial culture has been obtained [3, 4, 24].

CRP does not cross the placenta [12, 15, 21]. It is known to be produced in high concentrations as an acute phase reactant in term newborn infants with systemic bacterial infection [6, 14, 16]. It can also be found in children and adults with a great variety of inflammatory or destructive processes [5, 7, 8, 9, 11, 13, 18, 19, 20, 22]. Healthy newborns have low levels of CRP which are not detectable with semi-quantitative methods [2].

Our aim was to find out whether CRP was a helpful tool in the early

diagnosis of sepsis of premature newborn infants whose immunologic competence and abilities of synthesis were still immature.

Patients and Methods

From January 1980 to May 1981 we measured CRP concentration of 100 infants admitted consecutively to our hospital. The babies' birth weight ranged from 830 g to 2500 g. In addition to immaturity, all babies had complications during pregnancy and/or in the perinatal period such as cervix insufficiency, rupture of amniotic membranes 24 h or more prior to delivery, EPH gestosis, amnionitis, maternal fever, postpartum asphyxia or hyaline membrane disease.

Serum CRP was measured by the radial immunodiffusion technique [1] using the LC-Partigen CRP kit (Behring-Werke AG, Marburg/Lahn). Serum standards were included in each run to construct a calibration curve for each set of unknown sera. The serum samples were stored in the frozen state until some had been accumulated, and were then thawed to measure CRP concentrations.

According to Sabel and Wadsworth [17] serum CRP concentrations ≥ 5 mg/l were considered to be normal. Values between 5 and 10 mg/l were considered to be equivocal. Levels ≤ 10 mg/l were deemed to be abnormal. Examinations were done daily as long as elevated CRP levels were found.

The diagnosis of septicaemia was supported by clinical signs of illness (bad general state, lethargy, temperature instability, pallor/jaundice, hepatosplenomegaly, etc.) as well as by diverse laboratory investigations including bacterial blood, urine and CSF cultures.

The diagnosis of bacterial infection was ensured by at least one positive bacterial culture (Group 1 patients).

Babies with clinical signs strongly suggestive of sepsis, but without positive cultures were "very probably" infected (Group 2 patients).

Finally, there were babies without clinical or laboratory findings of infection (Group 3 patients).

Results

6 out of 100 patients (4 male, 2 female) had a culture-proven sepsis (Group 1). 21 out of 100 patients (10 male, 11 female) had sepsis "very probably" (Group 2). 73 out of 100 patients showed no sign of illness (Group 3).

6/6 babies of Group 1 had elevated levels of CRP within 24 h after the first appearance of clinical symptoms. The mean peak values in this group (58.4 mg/l) were distinctly higher than in both other groups. Elevated CRP levels could be measured for 3.5 days. Under appropriate antibiotic therapy, and according to clinical improvement, CRP values changed promptly downward.

It is remarkable that one patient of Group 1 had a relapse after nine days of illness with recurrence of clinical symptoms and elevated CRP levels. Two babies of this group (Nos 3 and 4) had elevated CRP levels several hours before clinical signs had appeared (Table I).

11/21 patients of Group 2 ("very probable" infection) had elevated CRP levels. The concentrations rose to a mean peak value of 27.0 mg/l. CRP elevation was not so fast as in group 1. 8 babies had risen CRP levels within 24 h, one baby within 48 h, two babies within 72 h after the

TABLE I

Characteristics of patients with proven septicaemia

No.	Sex	Birth weight g	Age at onset of symptoms	Age at CRP rise day	Peak CRP value mg/l	Cause of infection
1. L. J.	♂	1770	<24 hours	1	47	Group B streptococci
			9 days	11	74	
2. U. S.	♂	1660	<24 hours	1	37	Groups B streptococci
3. K. M.	♀	2410	2 days	1	39	E. coli
4. H. M.	♂	1240	4 days	3	64	E. coli
5. L. A.	♀	2360	<24 hours	1	115	Group B streptococci
6. P. C.	♂	2320	<24 hours	1	33	E. coli

first clinical symptoms had appeared. CRP levels could be measured for 2 days. Only 2/73 patients of Group 3 (no sign of infection) had slightly elevated CRP for a short time.

Our studies showed that CRP levels are reflecting the course of infection: high levels are obviously combined with severe illness. CRP levels do not seem to be dependent of birth weight. Even a baby suspected of infection with a birth weight on 830 g was able to react with a CRP concentration of 22 mg/l.

DISCUSSION

The differential diagnosis and decisions on whether to start antimicrobial therapy in severely infected preterm infants are difficult. In our study, CRP, although a non-specific indicator, was a very reliable index in all cases of proven septicaemia as well as in many cases of suspected septicaemia. On the other hand, only two babies without signs of bacterial infection had slightly elevated CRP levels.

Theoretically, high CRP levels may also be caused by viral infections, effusions, or by inflammatory or non-inflammatory destructive processes. However, laboratory findings, clinical symptoms and improvement under antimicrobial therapy in our patients pointed to bacterial infection as the cause of CRP elevation.

We recommend the measurement of serum CRP as a valuable tool in the early diagnosis of sepsis in premature infants. It should be used more often in daily clinical practice.

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