Serial study of C reactive protein in neonatal septicaemia

P HINDOCHA, C A CAMPBELL, J D M GOULD, A WOJCIECHOWSKI, AND C B S WOOD

Academic Department of Child Health, Medical Colleges of St Bartholomew's and the London Hospitals, at Queen Elizabeth Hospital for Children, London

SUMMARY Serial C reactive protein concentrations were assayed by electroimmunoassay in 41 infants. Values in most of the non-infected infants were below 0.3 mg/dl, the lower limit of detection of C reactive protein by electroimmunoassay. Eleven of 12 infants with proved sepsis (positive blood cultures) had significantly raised concentrations and one infant with recurrent pseudomonas chest infection had a raised C reactive protein concentration. High C reactive protein concentrations were also found in infants with suspected infection. Successful treatment was followed by a decrease in the C reactive protein concentration. Total white blood cell count was not as appropriate as C reactive protein determination in the early identification of bacterial infection in the newborn.

The early signs of neonatal sepsis may be insidious and non-specific and those of infectious and non-infectious processes are similar. It is desirable to give appropriate antibiotic treatment as early as possible to those infants who are infected and to avoid this in those who are not. A number of tests have been proposed as aids to early diagnosis such as neutrophil count, band count, and buffy coat film but none have been widely accepted among paediatricians as good indicators of sepsis. Increased C reactive protein production is a very early and sensitive response to most forms of microbial infection¹ and the purpose of this study was to find out if the serial determination of this would be helpful in early diagnosis.

Patients and methods

All the babies admitted to the neonatal intensive care unit of the London Hospital over a three month period were studied as a cohort. Of the original 63 infants in the prospective study, only 41 could be followed serially because the rest did not fulfil the following criteria: (1) in hospital for more than two days; (2) samples for blood culture and C reactive protein taken on same day; (3) samples taken before antibiotics had been given.

When a newborn infant with suspected septicaemia was identified, evaluation included a smear

of gastric aspirate for Gram stain and pus cells; white blood cell count and differential; platelet estimate; and blood, urine and cerebrospinal fluid cultures. Blood samples for C reactive protein estimation were collected once each day until convalescence from each baby. (Most babies were having blood samples taken more than once a day for other reasons.)

Infants with suspected infection presented with two or more of the following risk factors: (a) maternal fever and mother given antibiotics; (b) culture of β haemolytic group B streptococcus (*Streptococcus agalactiae*) from vaginal swab; (c) prolonged rupture of membranes (longer than 24 hours); (d) purulent liquor; (e) abnormal delivery; (f) birth asphyxia; (g) clinical signs of sepsis; (h) white blood count less than $10 \times 10^9/l$ on the first day of life and; (i) small for gestational age. All infants were treated with antibiotics.

Quantitative estimation of C reactive protein was carried out according to the method of Laurell.² Results were available within 3 to 4 hours of an electrophoretic run. A reference curve was prepared by serial dilution of the standard serum. All the assays were batched and assayed blind without knowledge of the clinical condition of the infant. Results did not, therefore, influence treatment decisions during the study. Data were analysed and matched retrospectively to the clinical, haematological, and bacteriological parameters.

Results

When the results were analysed it was found that the clinical course of 27 infants (4 term and 23 preterm) was without signs of infection; the C reactive protein concentrations in these infants are shown in Fig. 1. As may be seen from Fig. 1 most C reactive protein concentrations in the 27 infants who were not infected were less than 0.3 mg/dl, which is the lower limit of detection of C reactive protein by electroimmunoassay. There were a few instances, however, where these values were above 0.3 mg/dl. There was no correlation between gestational age and C reactive protein concentrations in preterm infants (gestational age between 26 and 37 weeks), nor was there any difference between the C reactive protein concentrations in four term and 23 preterm babies in this group.

At the time of diagnosis 11 of 12 infants (11 preterm and 1 term) with proved sepsis (positive blood cultures) showed considerably raised C reactive protein concentrations which decreased after the start of treatment in many cases (Figs. 2 and 3). One infant had leucopenia at the time of diagnosis. Total white blood cell count and neutrophil count were not comparable with C reactive protein as early indicators of neonatal infection (Table). Bacteriological confirmation was not obtained in four episodes of clinically evident infection in two preterm infants (gestational ages 26 to 30 weeks), but the C reactive protein concentration was raised during each episode, which lasted a few days (Fig. 4). The infant of 26 weeks' gestation presented with

Fig. 1 Serum C reactive protein concentrations in 27 newborn infants (23 preterm and four term) without proved or suspected infection. Most values are below the lower limit of detection (0.3 mg/dl).

Fig. 2 Serum C reactive protein concentrations in the first 6 of the 12 newborn infants (11 preterm and 1 term) with proved sepsis.

The arrows indicate the start of infection (positive blood culture). The different symbols indicate individual patients. In some cases two arrows are shown with subscripts 1, 2 on the same patient these indicate positive blood cultures on different days of life.

Fig. 3 Serum C reactive protein concentrations in second 6 of 12 newborn infants (11 preterm and 1 term) with proved sepsis.

The arrows indicate the start of infection (positive blood culture). The different symbols indicate individual patients.

hypothermia, a blood pH of 6.9, and increasing jaundice from day 2 to day 4 of life; apnoea and bradycardia were evident on days 5, 6, 8, and 9. Penicillin and gentamicin were given for five days and the clinical response to antibiotic treatment was reflected by falling C reactive protein concentrations. These values started to rise again from age 18 days, however, and remained high on days 19, 20, 21, and 22. The infant became severely apnoeic on day 19 and episodes of apnoea and bradycardia lasted until day 20. Antibiotics were again given from day 18 to 28. The infant of 30 weeks' gestation had recurrent apnoea on days 2, 10, and 22 of life together with bradycardia on days 10 and 22. The start of antimicrobial treatment was followed by a

Table Newborn infants with positive blood cultures

Patient No	Sex	Birthweight (g)	Age at diagnosis (days)	C reactive protein (mg/dl)	White blood cells ($\times 10^9/l$)	Neutrophil count ($\times 10^9/l$)	Organism cultured
1	F	1360	1	17	26.4	19.3	β haemolytic group B streptococcus*
2	M	1240	1	16	17.9	11.3	Enterococcus
3	F	1340	9	12	12.2	5.9	<i>Staph epidermidis</i>
4	F	1260	19	20	—	—	<i>Staph epidermidis</i>
5	F	1740	8	21	—	—	<i>P aeruginosa</i>
6	F	1740	11	14	10.4	—	<i>Staph epidermidis</i>
7	M	1120	13	13	20.4	—	<i>Staph epidermidis</i>
8	F	1615	18	13	27.1	16.3	<i>Staph epidermidis</i>
9†	F	3500	1	20	6.5	—	Enterococcus
10	F	1940	1	8	24.1	14	<i>Strep mutans</i>
11	F	1940	10	20	29.5	18.6	<i>Staph epidermidis</i>
12	M	1300	15	20	14.9	9	<i>Staph epidermidis</i>
13	F	1280	20	20	16.2	11.8	<i>Staph epidermidis</i>
14	M	1460	9	<0.3	12.2	—	<i>Staph epidermidis</i>

* Also isolated from tracheal aspirate.

† Term baby, others are preterm.

Fig. 4 Serum C reactive protein concentrations in two preterm infants (gestational ages 26 and 30 weeks) with clinically evident infection but no bacteriological confirmation.

Arrows indicate the time of the first symptoms. The subscripts 1, 2 indicate two episodes of clinically evident infection. The closed circle refers to the infant of 26 weeks' gestation and the open circle to the infant of 30 weeks' gestation.

reduction and normalisation of the C reactive protein concentrations.

Fig. 5 shows C reactive protein concentrations in a preterm infant of 33 weeks' gestation who presented with apnoea. The infant had recurrent chest infections due to *Pseudomonas aeruginosa*, which was isolated on several occasions from the thick purulent secretions in the tracheal aspirate. The initial infectious episode responded to penicillin and gentamicin with a reduction in the C reactive protein concentration accompanied by an improvement in the infant's clinical condition. Subsequent episodes of infection were unresolved, however, as evidenced by recurrent apnoea and isolation of *Pseudomonas*

Fig. 5 Serum C reactive protein concentrations in a preterm infant of 33 weeks' gestation with recurrent chest infections due to *Pseudomonas aeruginosa*.

The arrows indicate instances when *pseudomonas* was isolated from the tracheal aspirate.

aeruginosa on culture despite a change to carbenicillin and amikacin; C reactive protein values remained raised.

Discussion

The results obtained in this study suggest that C reactive protein concentrations determined by electroimmunoassay reliably indicate infection at an early stage. The C reactive protein concentration was significantly raised at the time of diagnosis in 10 preterm and one term infant with proved sepsis. This finding in newborn infants with proved sepsis agrees with other reported results.³⁻⁶ A similar pattern in C reactive protein concentrations was shown in one infant with recurrent chest infection due to *P aeruginosa*. In four other episodes of clinically diagnosed infection C reactive protein

concentrations were raised and although these patients may have had septicaemia, bacteriological confirmation was not obtained. Total white blood cell count was not comparable with C reactive protein as an indicator of early neonatal infection.

The serial study of C reactive protein concentrations is of considerably greater value than single estimations both in diagnosis and as a guide to treatment. Serial serum C reactive protein determinations fell rapidly in patients in whom treatment was successful. Of the 12 patients with positive blood cultures only one failed to show any concurrent rise in the C reactive protein concentration. The organism cultured in this infant was *Staphylococcus epidermidis* (found in the skin) and we believe this may have been a contaminant in blood culture thus explaining the failure in C reactive protein production.

In conclusion, this serial study provides additional support for the observations^{4,6} that the C reactive protein concentration is a very reliable indicator of infection in newborn infants. The principal drawback in using this as an indicator of neonatal sepsis has been finding a suitable assay that provides quantitative results within a short time; diagnostic tests that might influence treatment must be readily available, require a minimum of time to process, and be highly dependable. These criteria may be fulfilled by immunonephelometric procedures, although some sensitivity is sacrificed.⁷ Loss of

sensitivity, however, may not be such a disadvantage since very high C reactive protein concentrations that can be easily quantitated are produced by the infected infants.

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Correspondence to Dr P Hindocha, Academic Department of Child Health, Queen Elizabeth Hospital for Children, Hackney Road, London E2 8PS.

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