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Diagnostic Value of C-Reactive Protein in Premature Babies Weighing less than 1500 g

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Quantitative estimation of C-reactive protein was carried out in 34 premature infants weighing less than 1500 g. An increased value proved to be a sensitive indicator of infection. Higher values seemed to be more reliable than low ones. The clinical diagnosis showed a good correlation with CRP positivity and its quantitative value.

Early detection of infection in small premature babies is still a problem in neonatology. Rapid and reliable diagnosis is often difficult, history of pregnancy and the perinatal period, and clinical symptoms still play a decisive role [10]. The latter are not specific, therefore they are not always unequivocal. Differentiation between hyaline membrane disease, connatal pneumonia and intracranial haemorrhage may be often difficult. Many attempts all over the world have been directed to reliable diagnosis (screening programmes, infection workshops).

The mortality rate of cardiopulmonary disorders of low birthweight newborns has much improved; less progress has been achieved in the reduction of the mortality rates of babies weighing less than 1000 g at birth. LaGamma et al [11] have shown that 21 babies among 35 survivors beyond the 5th day of life plus 27 fatal cases had some kind of infection, mostly caused by E. coli, Staphylococcus epidermidis and Staphylococcus aureus. This also points to the importance of new methods in the early diagnosis of infection.

Immunological studies have played here an important part [4]. It has been amply confirmed that the premature baby is able to give an immune response to an antigen in the early postnatal period or even in utero [4, 6]. The so-called acute phase reactions are indicators of the nonspecific immune response. In this study we have examined the diagnostic value of one of these indicators, C-reactive protein (CRP), in premature infants weighing less than 1500 g at birth.

During the last decade many reports on CRP in infected newborns or young infants have been published [1, 2, 3, 5, 8, 15, 16, 24]. Information on newborns below 1500 g is, however, scarce [13]. It seemed reasonable to study this weight group.

Material and Method

During the period from March 1, 1981, to March 31, 1983, CRP was estimated in 34 newborn babies below 1500 g admitted to our department. 22 of them were ill, 12 appeared to be intact. Their gestational age ranged from 24 to 37 weeks, their weight from 600 to 1500 g. Determination of serum CRP was carried out during the first 48 hours after birth. The study was performed in a prospective manner. Allotting to either group, pathological or control, was carried out at the bedside.

CRP was estimated in a Beckman ICS I kinetic nephelometer. The maximum rate of antigen-antibody reaction is proportional to the concentration of human CRP. Time of measurement was 1 minute.

There is no unanimity in the literature as to the normal values. The capillary immune precipitation method, used initially [8] was later deplaced by the more accurate immune diffusion techniques [10, 12]. In 1984, Ewerbeck et al [7] reported on CRP values determined by this method in 100 premature babies weighing between 850 and 2500 g. Kinetic nephelometry is even more accurate and more rapid, the measurement takes 1 minute, therefore it is more useful in the rapid diagnosis of neonatal sepsis. Our patients were all smaller than 1500 g, i.e. this material was more uniform and represented a more vulnerable weight group. Quite obviously, we compared our results with normal values obtained by nephelometry [9], the value of 1 mg/dl was thus taken as a cutting point between normal and pathological.

Results

Tables I and II show some characteristics of 22 sick and 12 intact premature newborns weighing less than 1500 g. The proportion of very im-

Table I

Some data, clinical diagnosis, bacteriological findings and CRP positivity rates of premature babies of less than 1500 g birthweight

	Newborns with intrauterine infection	Controls
Number of cases	22	12
Birthweight, range	710—1500 g	600—1500 g
Gestational age, range	25—34 weeks	24—34 weeks
Sex, boys	10	2
girls	12	10
CRP, positive	20 cases (1.1—418 mg/dl)	5 cases (1.3—2.8 mg/dl)
negative	2 cases (0.3—0.6 mg/dl)	7 cases (0.4—0.7 mg/dl)
Diagnoses	Bronchopneumonia: 13 IRDS+atelectasis: 1 Prematurity: 5	Prematurity: 12
Bacteriological findings	Negative: 9 Positive: 13	Negative Positive
(nose, throat, external ear, umbilicus, stomach)	E. coli and Gram negative bacteria: 6 Staphylococcus aureus and Gram positive bacteria: 7	E. coli

TABLE II

Results of screening tests performed in patients suspect of infection or sepsis

Group	Number of patients	Number of patients with positive finding							
		History	CRP	IgM	C_3	Leukocytes	Bacteriology	Clinical symptoms	Blood smear
Infected	22	17	20	15	13	8	15	19	13
Control	2	5	3	6	2	2	3	7	0

mature babies, weighing less than 1000 g was rather high, there were 12 such infants in the whole material. There were more girls in both groups but in different proportions; in the sick group there were 12 girls against 10 boys, in the healthy group the ratio was 10 : 2. This can be explained by the well-known increased vulnerability and disposition to infection of premature boys. In the affected group an increased CRP value was found in 20 cases out of 22, a very good hit ratio. In the intact group only 5 CRP positive cases were found among 12 babies.

13 sick babies were affected by bronchopneumonia. In the remaining cases the X-rays suggested atelectasis, idiopathic respiratory syndrome or aspiration (see Table I). In these cases the elevated CRP revealed the infective nature of the disease; this was confirmed by further clinical observation and additional laboratory findings. The roentgenogram may not often be useful in clarification of the aetiology [3]. Five premature babies with clinical symptoms and laboratory findings characteristic of infection (they were also treated with antibiotics) were included into the group of infected babies although the site of infection could not be localised.

Bacteriological cultures from the nose, throat, external auditory canal, umbilicus and stomach were performed in all babies. In addition, direct bacteriological evaluation of a smear made of the gastric juice and the buffy coat was carried out. In 8 cases one pathogenic agent was cultured, two in 5 cases. 7 positive outer ear cultures were obtained, an important finding in the bacteriological diagnosis of intrauterine infection. A positive bacteriological culture does not necessarily mean infection. Therefore, a decision for colonisation, contamination or infection was made after considering the results of all tests listed in Table II.

Figures 1 and 2 show the quantitative results of CRP estimations. In Figure 1 the mean of all positive cases included in the analysis (= 7.035 mg/dl) and the highest value after exclusion of extremely high values are indicated. Two very high values were excluded from the analysis: one value of 160 mg/dl — a Shirodkar operation had been carried out in the mother of this baby one month before labour —, and one

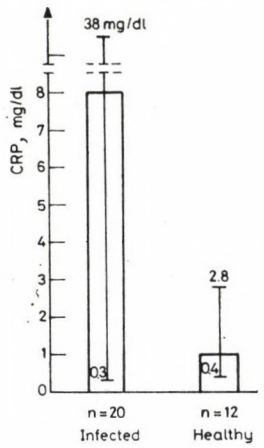

FIG. 1. Mean and range of CRP values in infected and healthy prematures CRP, mg/d

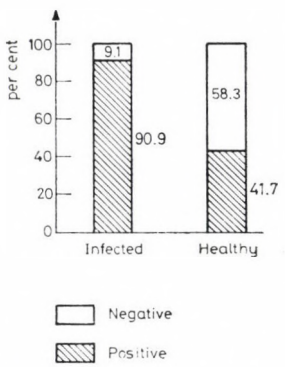

FIG. 2. Percentual proportion of positive and of negative CRP findings in infected and healthy prematures

value of 418 mg/dl, in this case the membranes had ruptured one month before birth. The mean value of intact babies was 1.07 mg/dl. Thus, the degree of elevation within the range of increased values has also to be taken into consideration when evaluating the individual result.

In Figure 2 the percentage of positive and negative results is shown. In the infected group CRP was increased in 91% of cases, in the healthy group in 42%. In view of the high participation of infection in perinatal mortality of premature infants, the risks of "superfluous" treatment are smaller than those of overdue intervention. False positive CRP findings among healthy babies are thus the smaller evil.

DISCUSSION

Table II illustrates our strategy of screening for neonatal sepsis. The relative importance of the exact history and clinical findings is obvious. CRP and quantitative IgM appear to

be the most reliable among the rapid laboratory tests. We examined how far there was a concordance between CRP positivity and the diagnosis. A fairly good correlation between CRP positivity and infection (correlation coefficient = 0.5) and the degree of elevation and infection (correlation coefficient = 0.4) was found. In our present practice, antibiotic treatment is initiated whenever at least three positive findings are present.

Although the CRP level is elevated in most pregnant mothers, the blood of the healthy newborn contains no or negligible quantities of CRP at birth [8, 10, 15]. By the end of the first week there is a slight increase, no pathological levels are, however, attained in healthy infants. It may be concluded that this protein does not cross the placenta. In newborns with premature rupture of the membranes or suspect of being infected, increased CRP values have been found [10, 14]. This speaks for the idea that CRP production can be stimulated as early as in the newborn period.

In the uninfected group positive clinical findings can be encountered. This is striking but not unexpected since a premature baby may be sick without being infected. A good example is intracranial haemorrhage. Rapid diagnosis of infection is a matter of life and death.

Our results suggest that nephelometric estimation of CRP in premature newborns is a valuable step towards early diagnosis of infection and, consequently, to effective treatment.

References

1. Alistar GSP: The protective effect of acute phase reactants in neonatal sepsis. Acta Paediatr Scand 68:481, 1979
2. Alistar GSP, Hevitt JR: Early diagnosis of neonatal sepsis. Pediatrics 65: 1036, 1980
3. Alistar GSP: Detection of neonatal sepsis of late onset. JAMA 247:489, 1982
4. Balla G, Karmazsin L: Evolution of serum C_3 IgA and IgM levels of healthy mothers and their mature newborns during the early neonatal period. Acta Paediatr Hung 24:41, 1983
5. Boyle RJ, Chandler PB, Stonestreet BS, Oh V: Early identification of sepsis in infant with respiratory distress. Pediatrics 62:744, 1978
6. Csorba S: Immunological status of preterm babies. In: Perinatal Medicine, eds Kerpel-Fronius E, Véghelyi PV, Rosta J. Akadémiai Kiadó, Budapest 1978
7. Ewerbeck H, Künzer W, Uhlig T: Serum C-reactive protein in early diagnosis of bacterial infections in premature infants. Acta Paediatr Hung 25:55, 1984
8. Felix SN, Nakajima H, Kagan BM: Serum C-reactive protein in infections during the first six months life. Pediatrics 37:270, 1966
9. Fischer LC: Quantitation of acute phase protein postoperatively. Am J Clin Path 66:840, 1976
10. Kindmark CO: The concentration of C-reactive protein in sera from healthy individuals. Scand J Clin Lab Invest 29:407, 1982
11. LaGamma F, Drusin LM, Nackles AW, Auld PM: Neonatal infections. Am J Dis Child 137:838, 1983
12. Mortensen RF, Gewurz H: Effect of C-reactive protein in the lymphoid system. J Immunol 116:1244, 1976
13. Nelson Textbook of Pediatrics 12. ed WB Saunders, Philadelphia 1983
14. Pilar de Pilar CE, Raschke P, Lischka N, Kreici K: Akute Phase-Proteine bei Früh- und Neugeborenen. Klin Pediatr 192:45, 1980
15. Sabel KG, Hanson LA: The clinical usefulness of C-reactive protein (CRP) determinations in bacterial meningitis and septicaemia in infancy. Acta Paediatr Scand 63:381, 1974
16. Sabel KG, Wadsworth C: C-reactive protein (CRP) in early diagnosis of neonatal septicaemia. Acta Paediatr Scand 68:825, 1979

17. Saxtad J, Nilsson LA, Hanson LA: C-reactive protein in serum from infants as determined with immunodiffusion techniques. Acta Paediatr Scand 59: 25, 1970
18. Wadsworth C: A rapid spot immunoprecipitate assay method applied to quantitating C-reactive protein in paediatric sera. Scand J Immunol 6:1263, 1977
19. Wauer RR, Herrmann H: Frühdiagnose neonataler Infektionen mit C-reactivem Protein (CRP). Kinderärztl Prax 50:752, 1982

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