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EARLY POSTNATAL CHANGES OF IMMUNOGLOBULIN LEVELS IN VERY LOW BIRTH WEIGHT ($\leq$ 1500 g) PRETERM INFANTS

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Immunoglobulin levels were measured in 16 very low birth weight preterm infants (birth weight: 1091±221 g, gestational age: 28.8±1.6 wks, mean±SD) at birth and at postnatal ages of 2, 4, 6 and 8 weeks. IgM level increased significantly by the age of 2 weeks (0.26±0.25 g/l vs 0.76±0.45 g/l, $p < 0.05$), then remained unchanged throughout the study period. IgA level did not change significantly. IgG level decreased significantly by the age of 6 weeks (6.04±3.8 g/l vs 4.4±1.4 g/l, $p < 0.05$), but after that no further decrease could be detected. The extent of the decrease in IgG level, however, proved to be smaller than expected on the basis of the reference data for term infants. The possibility is suggested that the packed red cell tranfusions given to the patients may have resulted in the higher immunoglobulin levels.

INTRODUCTION

Neonatal infection is one of the major factors determining the outlook for survival of very low birth weight (VLBW) preterm infants. In spite of the continuously improving armamentarium of antibiotics, neonatal infections still represent life-threatening complication of a variety of acute disorders of postnatal adaptation. Moreover, even successfully treated episodes of neonatal infection are known to contribute to the pathogenesis of such severe chronic diseases like broncho-pulmonary dysplasia and retinopathy of prematurity.

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Number of factors are well-known which determine whether a baby will or will not acquire infection during the perinatal period of life. Among these, the humoral immunity of the newborn infant plays an essential role.

Our present work was aimed to study the humoral immunity of VLBW neonates during the first 8 weeks of life. It is much debated in the literature whether preterm babies should or should not be given prophylactic immunoglobulin (IG) therapy. By following-up IG levels in our patients we attempted to determine the extent of the hypoimmunoglobulinaemia of these newborn infants.

PATIENTS AND METHODS

During the period from 1/05/87 to 30/10/87 all VLBW (birth weight $\leq$ 1500 g) neonates admitted to our Neonatal Intensive Care Unit within 24 hours of birth were enrolled in the study, provided that their hospital care lasted for at least 8 weeks. Those with congenital malformations and those having received double volume exchange transfusion were excluded but not the ones with any other kind of pathology. After all, 16 preterm babies (10 males and 6 females) with gestational age and birth weight (mean$\pm$SD, range in parantheses) of 28.8$\pm$1.6 (27 to 32) weeks and 1091$\pm$221 (770 to 1450) g, respectively, were studied. Six of the 16 patients were small for gestational age, by their characteristics and percentile position on the intrauterine growth chart used.

Blood samples were taken on admission and at the postnatal ages of 2, 4, 6, and 8 weeks. Immunoglobulin levels were measured by the radial immunodiffusion method of Mancini et al. /6/.

The patients were given neither immunoglobulin in bolus, nor plasma transfusions except one baby, who received because of septicaemia 2 ml Venagamma (HUMAN, Gödöllő, Hungary) with measured mixed IG fragment content of 0.12 g, and 30 ml of fresh plasma with measured IgG, IgA and IgM contents of 0.35, 0.02 and 0.02 g, respectively. On the other hand, all preterm infants except two, required packed red cell transfusions and, thus, altogether 26 packed red cell transfusions were given during the study period.

As for the diagnosis of infection, an infant was considered to be infected if the clinical signs were corroborated either by laboratory and/or bacteriological culture data or by the decision of the neonatologist to start antimicrobial treatment.

For statistical analysis the Student's t test was used.

RESULTS

Changes in IgG, IgA and IgM levels are shown in Table I. IgG level decreased significantly by the age of 6 weeks, then practically no further decrease could be observed. IgM level increased significantly by the age of 2 weeks, but later on no further rise could be detected. No remarkable change of IgA level was observed during the study period. It is to be emphasized, however, that due to the low neonatal serum levels and the relatively low sensitivity of the radial immunodiffusion method, both IgM and IgA levels should be evaluated with reservation since they represent the arithmetic mean of several low and only a few outstanding values /4/.

On Fig.1 the IgG levels measured in the present study are compared to the results published in two recent follow-up studies /1, 3/. The differences in absolute values may well be due to the different methods of determination. Ballow et al. used ELISA, whilst Conway et al. applied standard centrifugal fast analyzer. Nevertheless, the characteristic postnatal decrease in IgG level could be demonstrated in all three studies. The extent of the decrease, however, proved to be smaller than that seen in healthy, full-term newborn infants /7/.

Table II shows the impact of packed red cell transfusions on neonatal IG level. As it can be seen, IG levels in the blood products transfused were, on the average, 2 to 18 times higher than the neonatal serum levels measured 7 ± 7 days before the transfusion. The recommended volume of packed red cell transfusion is 15 ml/kg, whereas the circulating blood volume of the neonate is generally estimated to be 85 ml/kg. That is to say, the exogenous immunoglobulin intake by the packed red cell transfusion was well in the range of the actual amount of circulating immunoglobulins. The theoretical bases of the calculation of the transfusion-caused rise in neonatal IG levels have been reported in detail elsewhere /5/.

During the 8-week study period practically all newborn babies had at least one episode of infection. The mean number

TABLE I

Changes in immunoglobulin levels of very low birth weight preterm infants during the first 8 weeks of life (mean ± SD)

Age	(No.)	IgG (g/l)	IgA (g/l)	IgM (g/l)
0 to 24 hours	(16)	6.04 ± 3.80	0.22 ± 0.48	0.26 ± 0.25
2 weeks	(13)	5.29 ± 2.81	0.10 ± 0.29	0.76 ± 0.45+
4 weeks	(16)	4.88 ± 1.78	0.34 ± 0.40	0.69 ± 0.48
6 weeks	(15)	4.40 ± 1.40+	0.27 ± 0.26	0.59 ± 0.27
8 weeks	(16)	4.36 ± 1.26	0.30 ± 0.22	0.69 ± 0.24

+ = $p < 0.05$ when compared to the initial level

TABLE II

Impact of packed red cell transfusions (n=15) on immunoglobulin levels of very low birth weight preterm infants (mean ± SD)

	IgG (g/l)	IgA (g/l)	IgM (g/l)
Serum level before (7 ± 7 days) transfusion	4.56 ± 2.23	0.08 ± 0.14	0.50 ± 0.37
Immunoglobulin level in the units transfused	10.0 ± 3.40	1.43 ± 0.70	1.30 ± 1.65
Calculated rise of serum level	0.93 ± 0.40	0.14 ± 0.09	0.12 ± 0.15

of infectious episodes per patient was 1.3±0.6, i.e. it was in accordance with the data reported in the literature /1/.

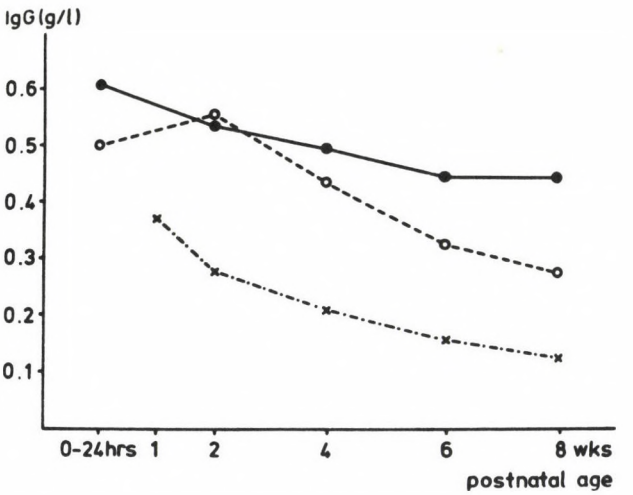

Fig. 1. IgG levels of very low birth weight preterm infants during the first 8 weeks of life. Results of the present investigation (——) are compared to the results of Conway et al. (---) and Ballow et al. (-o-o-o-).

DISCUSSION

During the past decades much has been learned about the humoral immunity of preterm infants. It is well documented that their IG levels are considerably lower than that of the term neonates. Moreover, it has also been demonstrated that IG levels at birth are directly proportional to gestational age /2, 8/. In the case of VLBW neonates, however, the improving survival rate has just recently rendered possible follow-up investigations to be carried out /1, 3/.

By following up IG levels in our patients we found somewhat higher values than expected (Table I). In case of IgA and IgM levels the differences may well have been due to the methodological difficulties mentioned previously. Nevertheless, due to their much higher absolute values IgG determinations are

certainly more reliable. In this case the extent of the decrease proved to be smaller than expected, though we could demonstrate the characteristic postnatal decrease well-known from the literature (Fig. 1).

One possible explanation for the higher IG levels may be the effect of transfusions. Nearly all VLBW neonates require packed red cell transfusions in the neonatal period, whereas term infants are seldom in the need of transfusion. Though it is declared even in paediatric textbooks /9/ that packed red cell transfusions contain no IG, but we were unable to find any data regarding actual measurements on the IG levels of units of packed red cells. Therefore, at 15 transfusions given to VLBW neonates we measured the IG content of the blood transfused, and IG levels were found to be much higher in the units transfused than in the serum of the neonates. The ratio of the blood product transfused to the circulating blood volume was approximately 1 to 6; so the packed red cell transfusions could rise considerably neonatal immunglobulin levels (at least up to the extravasal distribution of the immunoglobulins). On the basis of the results obtained it can be concluded that the VLBW preterm babies studied were less immunocompromised than suspected previously.

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