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Clinical correlations with immunoglobulin levels in newborns in a referral neonatal unit

II. Neonatal responses of immunoglobulins in full-term, preterm and dysmature infants admitted with suspected or proved infections

By

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The immunoglobulin levels of newborn infants admitted to a referral unit with suspected or proven infections have been evaluated according to maturity and intrauterine growth rate. The results showed that in the perinatal period the immunological response to infection is not dependent on gestational age and nutritional status. The dynamics of IgM observed in serial examinations showed essentially the same pattern in full-term, preterm and dysmature infants. It is concluded that in these three groups of infants, serum IgM concentration is a useful index in the diagnosis and screening of perinatally acquired infections. Quantitative measurement of immunoglobulins as a screening procedure is also useful in the selection of newborns with very low IgG values.

It is well-known that the foetus born at term is immunologically competent as far as its responses to antigenic stimuli are concerned [7]. Even premature infants, whose susceptibility to severe infections is one of the major handicaps in this group of newborns, are capable of responding by an increased synthesis of immunoglobulins [10]. It is a well-established fact that the level of serum IgG which crosses the placenta and reflects maternal levels, is closely related to gestational age [3, 6, 15, 18].

IgM and IgA on the other hand are not transferred from mother to foetus, and therefore high levels of these immunoglobulins indicate foetal production in response to intrauterine infection [2, 9, 14, 17].

The immunoglobulins of foetally malnourished infants have also been studied by different authors showing that in some of these abnormally low IgG concentrations may be observed [1, 4, 11, 16, 19]. Raised IgM levels have also been reported to be associated with intrauterine malnutrition which suggests that infection may be a responsible factor in growth retardation [19].

In order to study the immunological response to acute perinatal infections of full-term, preterm and small for dates infants the data obtained from the clinical material of a previous in-

vestigation [12] have been evaluated according to gestational age and intrauterine growth rate. The results are presented in this report.

Material and Methods

Serum immunoglobulin values for 120 infants have been analyzed according to maturity and intrauterine growth rate. The infants were divided into three groups: 1) full-term infants with a gestational age >37 weeks; 2) preterm infants with a gestational age <37 weeks; 3) dysmature infants whose birth weight fell below the 10th percentile of the respective gestational age. In some instances maturity was approximated by physical signs characteristic of the different stages of intrauterine development, and dysmaturity by the nutritional status of the newborn.

In addition to this material, the serum immunoglobulins of 30 neonates admitted with probable infections, and in whom two or more blood samples were collected at intervals from 6–10 days, were evaluated separately.

Gestational age was estimated from the date of the last menstrual period, and the rate of growth in utero by our local standard [5]. Serum was obtained from clotted venous blood taken from a cephalic vein, or withdrawn through an umbilical venous catheter within 24 hours of admission or of appearance of symptoms. Immunoglobulins G, A and M were quantitated by means of the method described by Mancini et al. [13] using specific antisera produced by Human, Budapest. IgG, IgA and IgM standards supplied by Behring were used.

Results

Immunoglobulin levels in full-term, preterm and dysmature infants admitted with suspected infections

The mean immunoglobulin concentrations obtained on admission in three groups of infants are shown in Table I. Preterm and dysmature in-

Table I

Immunoglobulin levels in full-term, preterm and dysmature infants admitted with suspected infections

		Full-term infants n = 69	Preterm infants n = 26	Dysmature infants n = 25
Gestational age	Mean	39.45	32.24	38.86
	Range	37–44	27–36	33–41
Birth weight	Mean	3089.13	2226.15	2394.0
	Range	2950–3500	1500–2950	1820–2960
	Mean	1179.08	904.15	1002.72
IgG	SE	± 46.33	± 86.81	± 85.54
	Range	480–1360	80–2240	96–1720
	Mean	13.18	23.46	21.96
IgA	SE	± 4.36	± 9.45	± 6.97
	Range	0–110	0–186	0–56
	Mean	73.05	81.57	94.08
IgM	SE	± 6.64	± 10.21	± 7.64
	Range	0–272	0–176	0–160

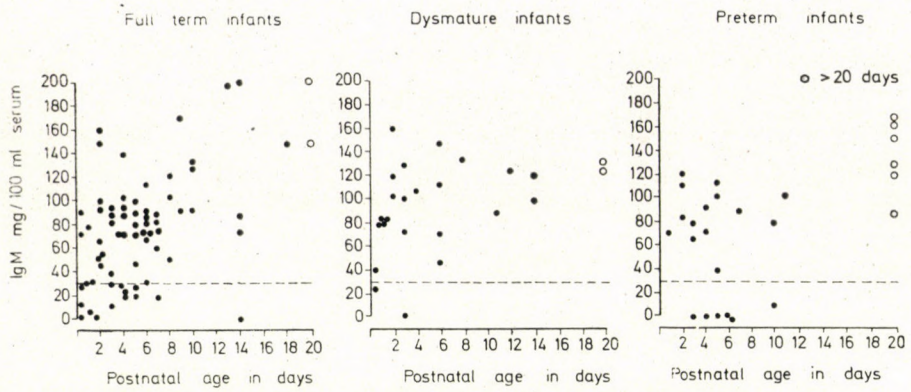

FIG. 1. Individual serum IgM concentrations in full-term, dysmature and preterm infants

fants had a significantly lower IgG level than the full-term infants, ranging from 80 to 2240 and 96 to 1720 mg per 100 ml, respectively. The mean IgM level was high in each group indicating that the majority of infants was infected at the time of serum collection; IgM was significantly ($p < 0.001$) lower in normally grown full-term than in dysmature infants. The individual IgM concentrations in the three groups of infants are shown in Fig. 1.

IgA was detected in 7 preterm, 8 full-term and 7 dysmature neonates. Half of these infants showed a considerably increased IgA level within the first week of extrauterine life indicating that infection had probably been acquired before delivery. Elevated serum IgA concentrations — as it is shown in Fig. 2 — were observed only in infants with high IgM levels, in agreement with the observation of ALFORD et al. [2].

YEUNG and HOBBS [19] found a significantly lower IgG level in the serum of small for dates infants on the first day of extrauterine life, and concluded that placental insufficiency might be responsible for its depletion. ADDY [1] could not confirm these observations, while PAPADATOS et al. [16] and JONES [11] reported that in some small for dates infants, such as those with a birth weight below the 3rd percentile, the IgG level was abnormally low. In the present series of examinations a tendency towards lower IgG values was undoubtedly observed. Fig. 3 shows the distribution of the individual levels in relation to the normal mean $\pm$ 2 SD corresponding to different postnatal ages. It can be seen that the great majority of IgG values were between the lines representing the mean and —2SD; in 7 dysmature babies IgG was present in quantities smaller than —2SD.

On the basis of these findings and those reported in the literature, it appears reasonable to assume that initial IgG levels below 600 mg per 100 ml can be a relevant factor in the

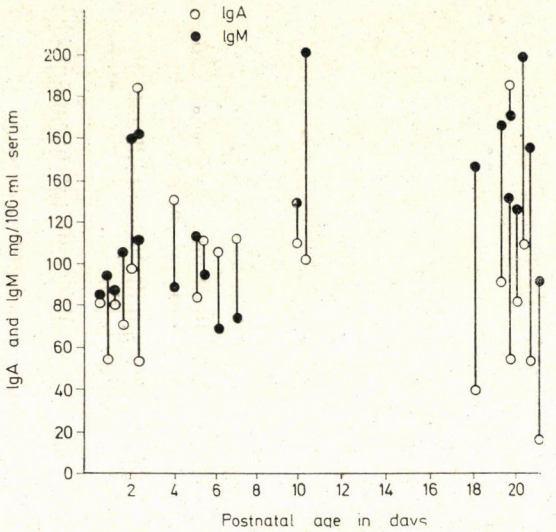

FIG. 2. Infants in whom high IgM levels were associated with high IgA levels

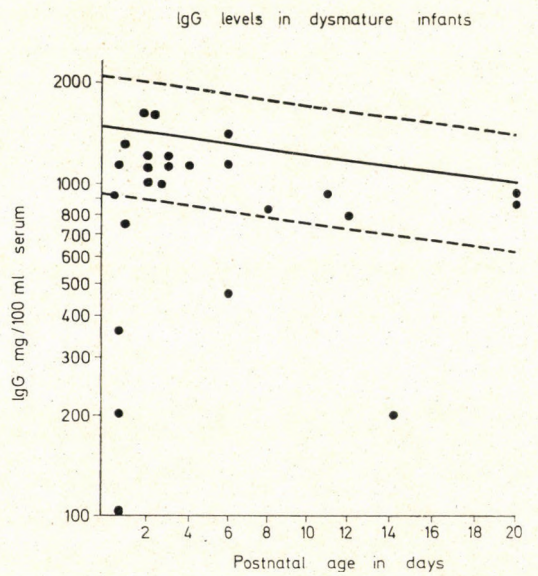

FIG. 3. Semilogarithmic plot of serum IgM values obtained in dysmature infants in relation to the normal mean ± 2 SD

susceptibility to infections in this category of newborns. The postnatal decline of IgG to very low levels may further increase the susceptibility to infections as it is commonly seen in premature infants born before 33 weeks gestation.

Intrauterine infection may be a causative factor in foetal malnutrition which is often reflected in an increased IgM concentration in cord serum. The pathological changes in the placenta have been incriminated both in the increased susceptibility to infections, and in the intrauterine immunological stimulation. Placental insufficiency owing to extensive infarction might influence the transfer of IgG from mother to foetus leading to dangerous low levels after birth, and/or might facilitate intrauterine infections, the antigenic stimulation resulting in increased foetal IgM synthesis [19]. It would seem of interest to carry out correlative studies on the relationship of placental pathology and foetal immunology to obtain more definite information on this matter.

Serial examination of the responses of immunoglobulins

The first test performed in 18 full-term, 6 preterm and 10 small for dates infants on the first day of admission was followed by a second, or third determination of serum immunoglobulins. The interval between two tests varied from one to six weeks, but in the majority of cases it was not longer than 10 days.

The relevant clinical and microbiological data of the three groups of infants are shown in Tables II—IV, and the behaviour of IgM is seen in Fig. 4. The dynamics of IgM showed essentially the same pattern in full-term, preterm and small for dates infants. In most cases of systemic or localized infections the response of IgM was significantly greater than the normal. The starting IgM level scattered widely, and in a number of cases the abnormally high level reached in a few days of extrauterine life was followed by a further marked increase during the course of illness. Since the behaviour of IgM did not essentially differ in the three groups of infants, in Fig. 5 the pooled serial values have been plotted against postnatal age which globally shows the rate of postnatal increase of the IgM concentration in the babies with suspected or proved infections.

In these serial examinations a response of IgA was seen in three full-term, in two dysmature and in three premature infants. Among these babies in three instances IgA was detectable in a considerable quantity at the first test performed within 7 days after birth. In the remainder, IgA was first detected two weeks after admission. This is in agreement with the observations of ALFORD et al. [2] who reported a lower rate of increase of IgA than of IgM after the onset of clinical infection.

The dynamic pattern of IgM in infected full-term and low birth weight neonates was examined by HAIDER [8] who showed that the con-

TABLE II

Relevant clinical data of full-term infants with two or more immunoglobulin determinations

Age at admission	Age at first test	History, clinical assessment, diagnosis	Laboratory evidence of infection
14 days	14 days	Enterocolitis. Acidosis. Signs of sepsis	Enteropathogenic E. coli isolated from faeces
1 day	1 day	Asphyxia. Premature rupture of membranes	Streptococcus isolated from CSF
4 days	4 days	Omphalitis. Meningitis	—
5 days	7 days	Pneumonia. Hyperbilirubinaemia. Pemphygoid. Exchange transfusion	Staphylococcus aureus haemolyticus isolated from cutaneous lesions
1 day	1 day	Aspiration of amnionic fluid. Pneumonia	—
4 hrs	5 hrs	Meningocele	—
7 days	8 days	Omphalitis. Hyperbilirubinaemia	—
5 days	6 days	Hepatosplenomegaly. Congenital heart defect. Suspected rubella infection?	E. coli isolated from urine
1 day	1 day	Hepatosplenomegaly. Conjugated bilirubinaemia. Neonatal hepatitis?	—
4 days	4 days	Hyperbilirubinaemia. ABO incompatibility. Pemphygoid. Omphalitis	Staphylococcus aureus haemolyticus isolated from skin lesions
3 days	3 days	Conjunctivitis. Enterocolitis. Abdominal distension	Streptococcus beta haemolyticus recovered from external auditory canal. Proteus recovered from conjunctival swab
5 days	5 days	Apnoeic spells. Hyperbilirubinaemia. Signs of sepsis. Pneumonia. Leukopenia. Thrombocytopenia	Enterococcus cultured from umbilical stump and blood
5 days	5 days	Hyperbilirubinaemia. ABO incompatibility. Exchange transfusion	E. coli recovered from urine
1 day	3 days	Unconjugated and conjugated bilirubinaemia. ABO incompatibility. Signs of sepsis. Hepatosplenomegaly	E. coli recovered from urine
4 days	4 days	Asphyxia. Aspiration of amnionic fluid. Hyperbilirubinaemia. ABO incompatibility. Pneumonia. Omphalitis	Staphylococcus aureus haemolyticus recovered from umbilical stump, and E. coli from bronchi
1 day	1 day	Hyperbilirubinaemia. Cyanosis. Apnoeic spells. Omphalitis. Exchange transfusion	E. coli recovered from umbilical blood
4 days	4 days	Enterocolitis. Hyperbilirubinaemia. Omphalitis	Staphylococcus aureus haemolyticus isolated from umbilicus
4 days	4 days	Hyperbilirubinaemia. Enterocolitis. Hepatosplenomegaly	—

TABLE III

Relevant clinical data of dysmature infants with two or more immunoglobulin determinations

Age at admission	Age at first test	History, clinical assessment, diagnosis	Laboratory evidence of infection
4 days	6 days	Direct bilirubinaemia. Pneumonia. Omphalitis	E. coli recovered from umbilicus
3 days	3 days	Rh and AO constellation. Hyperbilirubinaemia. Pemphygoid	Staphylococcus aureus haemolyticus recovered from skin lesions, and Enterococcus from blood
3 days	3 days	Hyperbilirubinaemia. Rh constellation. Signs of sepsis	E. coli recovered from blood
3 hours	1 day	Vesicular skin eruptions. Signs of sepsis	—
2 days	3 days	Signs of sepsis. Direct bilirubinaemia. Hypoglycaemia	E. coli recovered from urine, Staphylococcus aureus haemolyticus from blood
1 day	4 days	Asphyxia, acidosis, pneumonia. Signs of sepsis	—
3 days	3 days	Hyperbilirubinaemia	Staphylococcus aureus haemolyticus recovered from external auditory canal, umbilicus and cerebrospinal fluid
3 days	3 days	Pemphygoid. Enterocolitis. Hyperbilirubinaemia	Staphylococcus aureus haemolyticus recovered from external auditory canal, umbilicus and skin lesions
1 hour	6 days	Toxaemia Hypoglycaemia. Petechiae. Hyperbilirubinaemia	—
2 hours	2 hours	Asphyxia. Omphalitis. Pemphygoid	E. coli, Staphylococcus aureus haemolyticus, and Klebsiella recovered from urine and Staphylococcus aureus from skin

centration rose gradually after the onset of symptoms. HAIDER concluded that the increase of serum IgM was independent of birth weight, as he observed no significant difference between normal and low birth-weight infants. The present findings support HAIDER's conclusion inasmuch as full term, preterm and small for dates neonates were equally capable of IgM synthesis in early extrauterine life. The variability of the rate of increase in IgM concentration was also similar in the three groups of infants.

Since maturity and nutritional status of the newborn appear to be of little significance for the capacity of immunological responses to perinatal infections, the importance of factors on which the dynamics of IgM formation are primarily dependent, remains to be determined. The possible

TABLE IV

Relevant clinical data of preterm infants with two or more immunoglobulin determinations

Age at admission	Age at the first test	History, clinical assessment, diagnosis	Laboratory evidence of infection
4 days	4 days	Signs of sepsis. Pneumonia. Hyperbilirubinaemia. Hepatosplenomegaly	Staphylococcus aureus haemolyticus recovered from blood and umbilicus
7 hours	8 hours	Subluxation of knee. No definite sign of infection	—
2 hours	1 day	Pemphygoid. Hyperbilirubinaemia	Enterococcus, E. coli and Proteus recovered from skin lesions
1 day	6 days	Pneumonia. Abdominal distension. Acidosis. Asphyxia. Hyperbilirubinaemia	—
2 hours	3 hours	Aspiration of amnionic fluid. Enteritis. Omphalitis. Pemphygoid	Staphylococcus aureus haemolyticus recovered from external auditory canal, umbilicus and skin lesions
9 hours	10 hours	Hypoglycaemia. Asphyxia. Direct bilirubinaemia. Pneumonia. Conjunctivitis	Staphylococcus aureus haemolyticus recovered from conjunctival swab, E. coli from urine

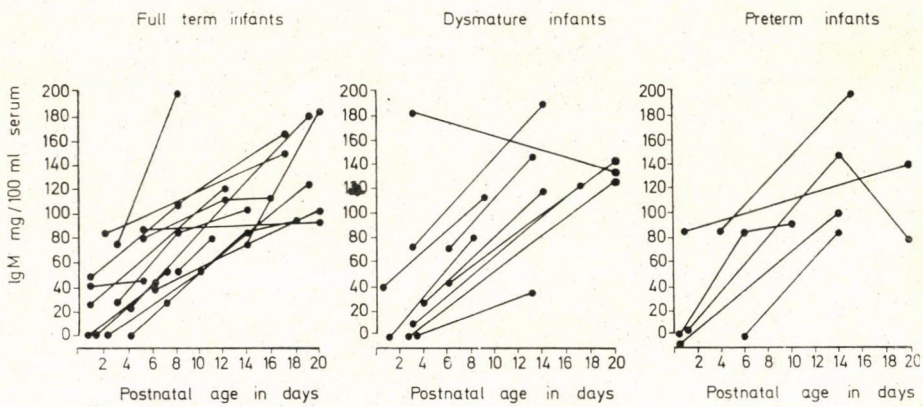

FIG. 4. Serum IgM levels in full-term, dysmature and preterm infants in whom two or more values were obtained

role of the nature of the microbial agents, the clinical types of infection, the severity of clinical damage and therapy has already been suggested by ALFORD et al. [2] and HAIDER [8]. Further correlative and serial investigations are, however, necessary to determine the relative importance of these factors in the variability of the rates of serum IgM and IgA synthesis in infected neonates.

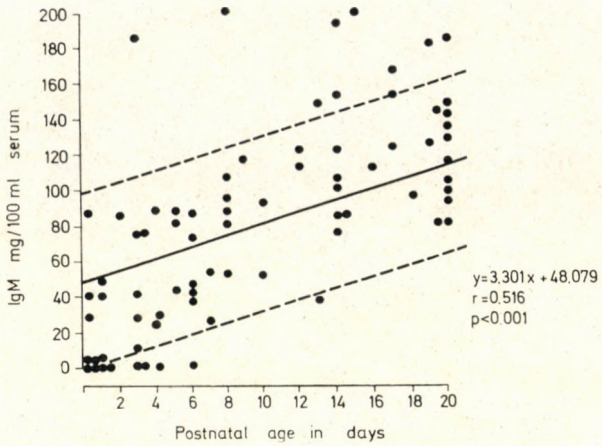

FIG. 5. Individual serum IgM levels obtained in serial examinations of full-term, dysmature and preterm infants, plotted against postnatal age. The correlation between the two parameters is highly significant

CONCLUSIONS

Evaluation of the IgM level according to gestational age and growth rate clearly shows that its response to perinatal infection does not significantly differ in the three groups of infants. In mature, premature and growth retarded neonates it is an equally useful index in the diagnosis and screening of acute, perinatally acquired infections. It appears that the immunological response to infection in the perinatal period is not so much dependent on gestational age and birth weight. Other factors such as microbial agents and duration of infection are probably more important in the elevation of the level of the serum immunoglobulins.

Since dysmaturity may be the consequence of chronic or subacute intrauterine infection, and infants with a birth weight below the 10th percentile often display abnormally high IgM levels, it seems reasonable to subject dysmature neonates to screening for intrauterine or perinatally acquired infections. Considering that there is a delay in the rise of IgM which may be followed by a similar response in IgA, it appears useful to follow the dynamics of the changes of immunoglobulins by serial examinations. A gradual rise or the persistence of high levels indicates an increased neonatal synthesis of these globulins. A fall of the initially increased concentrations suggests, however, the possibility of passively acquired immunoglobulins.

A response in IgA was less frequent, but where it was detected in a significant quantity, a markedly elevated IgM level could always be demonstrated. The combined occurrence of augmented and consistent IgM and IgA concentrations is of a great diagnostic significance in the case of

clinically inapparent or suspected infections.

A further advantage of the quantitative measurement of serum immunoglobulins as a screening procedure is that newborns with very low IgG values can also be selected. In such infants, like premature and some dysmature ones, a further marked postnatal fall in IgG concentration could easily endanger survival by an undue susceptibility to infections.

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