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THE SERUM IgG SUBCLASS LEVELS IN HEALTHY INFANTS OF 13—62 WEEKS OF AGE

B.J.M. ZEGERS [a,*], M. VAN DER GIESSEN [b], E.E. REERINK-BRONGERS [c] and J.W. STOOP [a]

[a] *University Children's Hospital Het Wilhelmina Kinderziekenhuis, Utrecht,* [b] *University Hospital Groningen and* [c] *Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam (The Netherlands)*

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Summary

The levels of IgG1, IgG2, IgG3, and IgG4 were determined in serum samples of 160 infants aged 13—62 weeks, and of their mothers. In addition the serum IgM, IgG, IgA, and IgD levels of the infants are presented. The results show that IgM, IgG1, and IgG3 slightly increase during the first year of life, whereas IgG2, IgG4, IgA, and IgD hardly do. This difference in the development of the various immunoglobulin isotypes reflects differences in the terminal maturation of subsets of B-lymphocytes into plasma cells. About 50% of the infants of this age had no detectable IgG4 and three children had no IgG2. These observations indicate that longitudinal investigations are needed in children suspected of a IgG2 or IgG4 subclass deficiency. No statistically significant influence of sex on the IgG subclasses could be demonstrated in these infants.

Introduction

In the past decade the quantitative determination of immunoglobulin (Ig) levels in serum and body fluids has developed into a routine test which can easily be performed in most if not all hospital laboratories. Efforts of the W.H.O. led to the establishment of international standards for the five major Ig classes and numerous studies concerning the influence of, e.g. age, sex, race, social class, on Ig levels have now been published [1,2].

Earlier studies in our laboratories included the quantification of IgM, IgG, IgA, IgD, and IgE in sera of healthy Dutch children of 4—13 years old as well as in adults [3,4]. Moreover, the levels of the four IgG subclasses in these sera have been published [5].

* Address for correspondence: Dr. B.J.M. Zegers, Department of Immunology, University Children's Hospital Het Wilhelmina Kinderziekenhuis, Nieuwe Gracht 137, 3512 LK Utrecht, The Netherlands.

Relatively few results are available concerning the development of the levels of the IgG subclasses during the first years of life [6,7,8]. It is the purpose of this communication to present the IgG1, IgG2, IgG3, and IgG4 levels as well as the IgM, IgG, IgA, and IgD levels of healthy Dutch infants aged 13—62 weeks in relation to the IgG subclass levels of their mothers.

Materials and methods

The serum samples of the present study were collected at a number of infant health centres of Utrecht. The infants visit these offices for a regular check-up of their physical and psychomotor development and for the administration of vaccines like diphteria, pertussis, tetanus toxoid and poliomyelitis (Salk) (DPTP), given at three, four, five and twelve months of age. The blood of the infants was withdrawn by a heel prick and from the mother by venapuncture. Informed consent was obtained in all cases. About 210 sera of infants and mothers were collected at random and seven age groups were composed each consisting of about 12 male and 12 female infants. The groups encompassed the age period 13—62 weeks.

The IgM, IgG, IgA, and IgD levels were determined as described earlier [3,4] by the radial immunodiffusion method of Mancini et al. [9]. The levels of IgM, IgG, and IgA are expressed in g/l using a control serum [4] which was standardized on the W.H.O. serum 67/86 [10]. The IgD level is expressed in I.U./ml using the same control serum standardized on the W.H.O. standard 67/37.

The IgG subclass levels were also determined according to the method of Mancini et al. [9] using antisera described earlier [11]. The results are in general expressed in percentages of the subclass concentrations of a standard serum (batch H00-01 of the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam) containing 121 I.U. of IgG/ml. This serum was checked against the control serum used previously [5], and contained 6.1 g/l IgG1, 3.2 g/l IgG2, 0.5 g/l IgG3 and 0.7 g/l IgG4. Statistical analysis, whenever relevant, was done essentially as described earlier [3,4].

Results

In a pilot experiment the possible influence of DPTP-immunization on the IgM, IgG, and IgA level was studied in four infants. The results disclosed that DPTP-immunization did not lead to a significant change in these Ig concentrations as determined 14 and 28 days after the first as well as after the second injection.

In Table I the arithmetic means, the standard deviation and the range of the serum concentrations of IgM, IgG, IgA, and IgG subclasses of the infants and their mothers are summarized, according to age. It is apparent from the table that IgM and IgG gradually increase between the 13th and 62nd week after birth, whereas the IgA concentration hardly does. Two children of 19 and 21 weeks of age had very low IgG levels of less than 0.20 g/l and eight infants had only traces of serum IgA (0.04 g/l or less). A significant influence of sex on the IgM, IgG, and IgA levels could not be demonstrated in our material.

With respect to IgD it was found that the number of sera with detectable IgD

TABLE I

SERUM IgM, IgG, IgA LEVELS (g/l) * AND IgG1, IgG2, IgG3, IgG4 LEVELS (IN PERCENTAGE OF A STANDARD SERUM) ** OF 160 CHILDREN IN THE AGE OF 13 TO 62 WEEKS AS WELL AS OF THEIR MOTHERS

Age (weeks)	No. of children	IgM range	S.D.	IgG range	S.D.	IgA range	S.D.	IgG1 range	S.D.	IgG2 range	S.D.	IgG3 range	S.D.	IgG4 range	S.D.
13—17	22	0.46 (0.28—0.75)	0.14	3.45 (1.80—6.05)	0.99	0.26 (0.09—0.55)	0.12	48 (26—76)	13.8	25 (7—50)	11.7	65 (28—128)	30.8	11 (<5—63)	9.1
17—21	23	0.49 (0.22—0.92)	0.20	2.93 (0.15—5.87)	1.43	0.25 (<0.04—0.63)	0.15	46 (14—84)	17.6	26 (<5—50)	11.0	80 (25—174)	40.4	10 (<5—40)	8.3
21—25	24	0.55 (0.13—0.94)	0.20	3.37 (0.17—5.63)	1.75	0.27 (<0.04—0.64)	0.17	51 (26—90)	19.5	26 (12—58)	9.9	74 (30—165)	39.1	9 (<5—27)	4.8
25—29	23	0.64 (0.25—1.26)	0.23	3.39 (0.93—7.25)	1.50	0.26 (0.09—0.63)	0.12	55 (37—136)	20.8	25 (12—65)	10.0	89 (31—214)	45.1	7 (<5—16)	4.0
29—47	24	0.84 (0.34—2.25)	0.40	4.47 (2.23—8.05)	1.53	0.30 (<0.04—0.64)	0.17	66 (28—134)	26.0	26 (<5—54)	12.8	104 (31—232)	55.4	8 (<5—16)	3.7
47—53	20	0.88 (0.57—1.37)	0.23	5.20 (3.02—8.65)	1.41	0.39 (0.18—0.90)	0.20	77 (39—136)	24.4	31 (13—59)	12.3	86 (33—200)	40.5	13 (<5—47)	8.7
53—62	24	0.87 (0.40—1.25)	0.25	5.23 (2.67—8.80)	1.44	0.36 (0.06—1.51)	0.26	79 (40—150)	25.1	39 (11—89)	22.0	76 (44—140)	18.8	10 (<5—32)	9.4
Mothers	160							114 (32—320)	34.3	121 (35—320)	51.8	151 (22—360)	64.5	74 (<5—408)	70.1

* According to W.H.O. recommendations [10] 1 mg IgG corresponds to 124 I.U., 1 mg IgM to 118 I.U., 1 mg IgA to 70 I.U.

** This standard serum contains 121 I.U. IgG/ml, and 6.1 g/l IgG1, 3.2 g/l IgG2, 0.5 g/l IgG3 and 0.7 g/l IgG4.

TABLE II

MEAN IgG SUBCLASS LEVELS IN g/l OF INFANTS AGED BETWEEN 13 AND 62 WEEKS COMPARED TO THE MEAN LEVELS OF CHILDREN OF 4—13 YEARS AND ADULT CONTROLS

	IgG1	(S.D.)	IgG2	(S.D.)	IgG3	(S.D.)	IgG4	(S.D.)
infants, 13—62 weeks	3.7	(1.5)	0.95	(0.45)	0.4	(0.2)	0.1	(0.1)
mothers	7.0	(2.1)	3.9	(1.7)	0.75	(0.35)	0.5	(0.5)
children, 4—13 years *	6.8	(1.85)	1.8	(0.55)	0.55	(0.25)	0.4	(0.35)
adults *	7.1	(1.65)	3.8	(1.1)	0.7	(0.35)	0.6	(0.4)

* See reference [5].

levels (i.e. higher than 4 I.U./ml) increases with age: the IgD levels of infants of less than six months old are in general lower than 4 I.U./ml, whereas in the second half of the first year 25 sera out of 92 showed a substantial amount of IgD, ranging from 4—44 I.U./ml.

Concerning the IgG subclass concentrations it appears from Table I that there is a slight increase of IgG1 and IgG3 concentration with age, whereas IgG2 hardly increases and IgG4 does not. All infants had detectable IgG1 and IgG3, three infants had undetectable IgG2 (i.e. lower than 5% of the level of the standard serum) and about 50% of the infants had undetectable IgG4. Two mothers had also undetectable IgG4. A statistically significant influence of sex on the IgG subclass levels could not be demonstrated.

Table II shows the mean subclass levels of the infants and mothers of the present study compared to those of healthy children of 4—13 years of age and of healthy controls studied earlier [5]. The results show that the arithmetic means of the subclass levels of the infants are lower than the levels of the adults.

Discussion

The results of the quantification of the Ig levels in the sera of the various groups of infants show the well-known rise of IgM and IgG and the almost stationary low amount of IgA during the first year of life. As far as serum IgD is concerned, the levels obtained confirm the observations of Geny et al. [12], indicating the presence of very low levels during the first half year of life. In a previous study [4], it was shown that even some adults (6.6%) had IgD levels of less than 4 I.U./ml, indicating that low serum IgD levels in childhood may persist during adult life. Recent findings of Dunnette et al. [13] disclosed that low IgD levels in man are inherited as an autosomal recessive trait.

With respect to the IgG subclasses it was shown that IgG1 and IgG3 increased slowly and that IgG2 and IgG4 remained low during the first year of age. These findings are in agreement with those of Morell et al. [6], Oxelius [7] and Schur et al. [8], and it was previously shown in a study of a group of children of 4 to 13 years of age that the latter subclasses still had not reached the adult level at the age of 12 (illustrated in Table II) and reference [5]).

From our study on the development of the serum Ig isotypes throughout the first decades of life it is apparent that there is a difference in maturation

of the synthesis of IgM, IgG1, and IgG3 on the one hand and IgG2, IgG4, IgA, and IgD on the other hand. The various immunoglobulin isotypes originate from distinct B cell precursors identified as bearing the appropriate isotype on their membrane together with IgD [14]. At birth the distribution of these B cell subsets in blood and bone marrow is almost equal to that in adults [15]. The difference in the development of the concentration of the immunoglobulins of the various classes should be based therefore on differences in the terminal differentiation of B cell subsets into plasma cells.

A number of specific antibodies are localized in distinct IgG subclasses, e.g. antibodies against polysaccharides are preferentially found in the IgG2 subclass [16]. However, IgG subclass deficiency does not necessarily lead to severe disturbances of humoral immunity and therefore it is worth-while extending our knowledge of serum IgG subclass levels in patients and documenting carefully the clinical findings in patients with deficiencies of one or more IgG-subclasses [17,18]. As far as infants or children are concerned it should be stressed that in view of the slow maturation of IgG2, and IgG4, repeated investigation is needed in case such a subclass deficiency is considered to exist.

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