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IMMUNOGLOBULIN ISOTYPES AND IgG SUBCLASSES IN RECURRENT INFECTIONS*

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The frequency of major immunoglobulin isotype and IgG subclass deficiencies among 74 children aged six months to 14 years with recurrent infections was studied. All children had at least five to six episodes of respiratory tract infections, while recurrent diarrhea had occurred in eight. Two selective and six partial IgA deficiencies were detected. IgG4, IgG3 and IgG2 deficiencies, either isolated or combined, were found in 13, nine and one patient respectively. Among these there were two combined deficiencies of IgA + IgG4, three of IgA + IgG3, one of IgA + IgG2 + IgG4, one of IgG1 + IgG3 and two of IgG1 + IgG4. There was one patient with panhypogammaglobulinemia. Our results, similar to those of other studies, showed that the occurrence of the Ig isotype, particularly subclass deficiencies, is not uncommon in children with frequent infections. *Key words: recurrent infections, Ig isotypes, IgG subclass.*

Recurrent infection is a relatively common problem in pediatric practice. Primary B-cell immunodeficiencies are associated with recurrent or chronic bacterial infections involving notably the respiratory tract and/or gastrointestinal system[1, 2]. The most common abnormality among primary B-cell immune deficiencies is selective IgA deficiency. The disease is characterized by its clinical variability associated with allergic, hematologic and autoimmune diseases, malignancies and other imunodeficiencies, and can be detected even in asymptomatic individuals[3, 4]. On the other hand, IgG subclass deficiencies account for recurrent infections in some children with or without major immunoglobulin deficiencies[5-9].

IgA deficiency is the most common one to be accompanied by IgG subclass deficiency[10, 11]. The purpose of the present study was to evaluate immunoglobulin isotypes and IgG subclasses in patients with recurrent sinopulmonary infections.

Material and Methods

Seventy-four patients, 40 boys (55%) and 34 girls (45%) between six months and 14 years in age (mean four years), who were admitted to the pediatric outpatient clinic between February 1994 and April 1995 were included in the study. Twenty-three out of 74 had a history of seven to eight episodes of upper and lower respiratory tract infections (URTI, LRTI) including sinusitis, otitis,

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tonsillitis, pharyngitis, laryngitis and pneumonia. Additionally, eight of these 23 patients had frequent diarrhea. Fifty-one patients out of 74 had a history of five to six episodes of URTI and LRTI. In this group seven patients also had a history of one of the following disorders: septic arthritis, abetalipoproteinemia, pulmonary tuberculosis, sepsis and asthma (in two).

All patients were tested for serum immunoglobulin levels and complete blood count (CBC). Major immunoglobulin classes (IgG, IgA, IgM) and IgG subclass levels were measured by radial immunodiffusion using the plates and reference sera of Behringwerke AG, Marburg, Germany and Binding Site Ltd, Birmingham, UK, respectively. When low concentrations were detected in the first measurement, it was repeated to confirm its accuracy. Immunodiffusion ring diameters were read on the electronic rid-reader (Binding Site Ltd, Birmingham, UK). The serum IgA concentrations below the limit of detection of standard immunodiffusion plates were retested by means of low level plates (Behringwerke AG, Marburg, Germany, LC partigen).

Age-stratified normal values for IgG, IgA, IgM, and IgG subclasses in healthy Turkish children were used as controls[12, 13]. This age-appropriate range was established in a healthy population, except for IgG[4]. Patients with serum IgA levels of less than 0.05 g/L, and serum IgA levels below two standard deviations (2SD) but above 0.05 g/L were accepted as selective and partial IgA deficiency, respectively.

For IgM, IgG and IgG subclass levels, patients who had levels below 2SD of normal values for his/her age were considered to be deficient. Patients with IgG4 concentrations equal to or below an arbitrarily chosen value of 0.03 g/L were accepted as deficient.

Results

The sum of IgG1, G2, G3 and G4 subclasses correlated well with the total IgG concentration (linear regression analysis, $r = 0.88$; $p < 0.001$). Various major immunoglobulin isotypes and/or IgG subclass deficiencies were found in 26 of 74 patients (35%) studied (Table I). One patient (no. 26) had panhypogammaglobulinemia. Low IgG levels were observed in two patients (nos. 24, 25); one had mainly decreased IgG1 and IgG3 concentrations, and the other decreased IgG1 and IgG4 levels.

Selective IgA deficiency occurred in two children (2.7%) combined with IgG3 deficiency in one and IgG4 deficiency in the other (nos: 1, 2). There were six patients with partial IgA deficiency (8%), three of whom also had IgG subclass deficiencies (nos: 3-8). Deficiency of IgG4 was found in 13 patients (17.5%); nine of these (nos: 14-22) were isolated. Two patients with IgG4 deficiency combined with IgG1, one with selective IgA deficiency and one with partial IgA + IgG2 deficiency (the only IgG2 deficiency found) were detected. There were nine IgG3-deficient patients (12%), five isolated (nos. 9-13) and four combined (nos. 1, 6, 7, 25) with IgA, IgG1 or IgG4. No lymphopenia or leukopenia was detected in any patient.

Table I: Clinical Features and Serum Immunoglobulin Levels (g/L) of Children with Immunoglobulin Deficiencies

Patient No.	Age (Months)	Clinical Presentation	Deficiency	IgA	IgM	IgG	IgG1	IgG2	IgG3	IgG4
1	42	RSP	S-IgA+G3	< 0.05	1.52	10.70	9.72	0.96	0.22**	0.21
2	36	RSP	S-IgA+G4	< 0.05	2.26	9.63	6.36	1.26	0.46	0.01x
3	32	RSP	P-IgA	0.17*	1.38	9.08	6.88	1.26	0.46	0.11
4	84	RSP	P-IgA	0.50*	1.60	12.50	9.42	1.80	0.41	0.57
5	108	RSP, Asthma	P-IgA	0.50*	0.77	8.55	5.37	1.92	0.88	0.27
6	20	RSP, ROM	P-IgA+G3	0.15*	1.99	8.02	6.36	1.16	0.24**	0.06
7	36	RSP, GE	P-IgA+G3	0.18*	1.84	10.70	8.83	0.67	0.28*	0.34
8	24	RSP	P-IgA+G2+G4	0.17*	0.89	7.00	5.37	0.22**	0.48	0.00x
9	24	RP	IgG3	1.09	1.45	10.70	7.15	1.26	0.26**	0.34
10	72	RSP, Giardias	IgG3	1.71	3.09	9.63	6.60	1.47	0.26**	0.31
11	36	RSP	IgG3	0.62	1.60	9.08	7.69	1.47	0.22**	0.16
12	168	RSP	IgG3	2.41	1.76	9.08	5.13	1.69	0.34**	0.06
13	16	RSP	IgG3	0.21	0.65	6.02	4.43	0.76	0.002**	0.15
14	9	RSP	IgG4	0.77	2.52	13.7	11.30	0.67	0.63	0.03x
15	10	RSP, ROM	IgG4	0.70	3.81	8.55	7.97	0.68	0.74	0.01x
16	36	ROM	IgG4	0.93	1.09	11.30	6.10	1.26	0.72	0.03x
17	18	RSP	IgG4	0.77	4.83	10.70	9.12	0.68	0.44	0.01x
18	15	RSP, ROM	IgG4	2.20	3.59	14.30	9.72	1.26	0.64	0.00x
19	36	RSP	IgG4	0.85	1.76	12.50	4.43	0.76	0.53	0.01x
20	6	RSP	IgG4	0.12*	1.38	5.08	3.99	0.68	0.50	1.01x
21	6	RSP	IgG4	0.16*	2.71	7.00	4.43	1.69	0.82	0.01x
22	10	RSP	IgG4	0.15	2.61	7.51	6.10	0.68	0.85	0.03x
23	24	RSP, ROM	IgG1+G4	1.09	2.00	6.51	3.57*	0.96	1.20	0.02x
24	48	RSP, ROM	IgG, G1+G4	0.55	1.16	5.55*	3.78*	0.76	0.48	0.03x
25	11	ROM	IgG, G1+G3	0.42	0.65	2.91**	2.02**	0.67	0.16**	0.04
26	33	RSP, ROM, GE	Hypo	0.13*	0.53*	3.32**	2.20**	0.25**	0.43	0.01x

RSP : recurrent sinopulmonary infection
GE : gastroenteritis
ROM: recurrent otitis media
S : Selective
P : Partial

Hypo : hypogammaglobulinemia
* : two standard deviations below the mean
** : three standard deviations below the mean
x : serum IgG4 level ≤ 0.03 g/L

Discussion

Children who experience recurrent or chronic respiratory tract or other infections pose difficult problem[8] for parents and pediatricians. A careful history, physical and laboratory examination, and review of medical records are very important in the evaluation of these patients.

This study demonstrated a high proportion (35%) of cases with various immunoglobulin deficiencies. A higher percentage of immunodeficiency among recurrent infections was reported in the studies of Gross et al.[14] and Moss et al.[15] In terms of deficient immunoglobulin isotype, Gross et al.[14] found 33 percent IgA, 10 percent IgG4, 6 percent IgG3 and 13 percent IgG2 deficient patients, while Moss et al.15 reported that IgG4 deficiency (17%) was the most common followed by IgG1 (6.5%) and IgG2 (6.5%). Surprisingly, only three IgA-deficient cases in a group of 123 patients with recurrent infections were detected in Moss's[15] study. The most common abnormalities in our patients were IgG4 (17.5%) and IgA (10.8%) deficiencies. These ratios of IgG4 and IgA deficiencies are very similar to the findings of Moss et al.[15] and Gross et al.[14], respectively. In the majority of studies, IgG4 deficiency was found to be common[8, 14-16]. But it should be emphasized that because a very low IgG4 level, particularly with radial immunodiffusion, can be detected even in healthy subjects (ranging from 7-30%), it is difficult to consider these patients as IgG4-deficient[15, 17, 18]. We found two selective and six partial IgA deficiencies in 74 patients. Concurrent deficiency of IgG3 occurred in two IgA-deficient patients in this study. There was also one patient with a combined deficiency of partial IgA-IgG2 + IgG4. IgG2 deficiency is the most common subclass deficiency that may be associated with IgA deficiency in most reports[10, 11, 17, 19-21]. However, we detected only one patient with a combined deficiency of IgA + IgG2 who was also IgG4 deficient. The frequency of IgG3 deficiency accompanied by IgA deficiency was also high (2/8) in this study, unlike in similar previous studies[10, 11, 17, 18, 21].

Although the exact cause of the concurrence of IgA and IgG subclass deficiencies is not well understood, it might be related to the close linkage of the genes that encode these heavy chains[6].

IgG subclass concentrations lower than 2SD below the mean for age-matched normal levels are accepted as subclass deficiency in most reports (as in ours) while others define this situation when the concentration is less than 3SD[14, 15, 18]. We detected nine (12%) cases of IgG3 deficiency (five isolated and four combined), which is the second most common IgG subclass deficiency followed by IgG4. This finding is also similar to the results of Gross et al.[14] We observed a low level of total IgG, primarily IgG1 (below 2SD) in three patients (nos: 23-25). Further studies could not be performed to determine the nature of the primary

defect in these three and the hypogammaglobulinemic patients. Except for these four patients, in all age groups the mean IgM, IgA and IgG concentrations tended to be higher than those of healthy subjects, probably due to recurrent infections.

In patients with IgA and subclass deficiency, serum IgA and IgG subclass levels may show a considerable increase with age[22,23]. Therefore, measurement of serum Ig levels at periodic intervals is necessary.

The true prevalence of IgG subclass deficiency is unknown. Controversy exists concerning the frequency of immunoglobulin subclass deficiencies in various studies. This may be due in part to differences in the method used for measurements, cut-off levels and clinical heterogeneity of the patients included in the studies. Children and even adults with recurrent infections should be evaluated for Ig isotype deficiencies, which are not so rare.

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