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THE FREQUENCY OF IgG SUBCLASS DEFICIENCY IN CHILDREN WITH RECURRENT RESPIRATORY INFECTIONS*

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SUMMARY: Güneşer S, Antmen B, Altıntaş D, Yılmaz M. (Allergy and Immunology Unit, Department of Pediatrics, Çukurova University Faculty of Medicine, Adana, Turkey). The frequency of IgG subclass deficiency in children with recurrent respiratory infections. Turk J Pediatr 1996; 38: 161-168.

We studied the frequency of IgG subclass deficiency in 61 children (ages 1-7 years, mean 3.8 years) with recurrent respiratory tract infections by using the radial immunodiffusion method. The overall frequency of IgG subclass deficiency was found to be 39.3 percent (24 patients). Among 26 children who had major immunoglobulin abnormalities, we found IgG subclass deficiency in 11 patients (42.3%). In children with normal immunoglobulin levels, the frequency of IgG subclass deficiency was 37.1 percent (13 patients). *Key words: IgG subclass deficiency, recurrent infections.*

Recurrent infections have been associated with agammaglobulinemia, hypogammaglobulinemia and IgG-subclass deficiencies[1]. IgG-subclass deficiencies have been described in patients with common variable hypogammaglobulinemia, ataxia telangiectasia[4], the Wiscott-Aldrich syndrome[3] and IgA deficiency[2]. More recently IgG-subclass deficiencies have also been reported in patients with hypergammaglobulinemia[5], recurrent bronchitis[6], acute myeloid leukemia[7], corticosteroid-dependent reversible airway obstruction[8], and obtructive lung disease[9]. In addition, impairment of the antibody response to specific microbial antigens predisposes patients with selective IgG-subclass deficiencies to recurrent infections[10].

The incidence of IgG-subclass deficiency has been reported in few studies among pediatric patients. In this study, we determined the frequency of IgG-subclass deficiency in pediatric patients with recurrent respiratory infections.

Material and Methods

Patients: This study included 61 children with recurrent respiratory tract infections. The mean age of the patients was mean 3.8 ± 2.0 (1-7) years. Of the 61 patients, 43 (70.4%) were male and 18 (29.5%) were female.

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All of the patients had been referred to the Pediatric Allergy and Immunology Department because of recurrent respiratory tract infections. Fourteen patients had had at least four episodes of otitis media, and 25 patients had experienced three episodes of upper respiratory infections including sinusitis. Seven patients had had at least four episodes of otitis media together with pneumonia. Twelve patients had suffered from at least three episodes of recurrent pneumonia. Recurrent sinopulmonary infections were associated with bronchiectasia in three patients. Thirty-two patients (52.4%) were found to be atopic (Table I). All patients had been seen by their pediatricians, and many had also been examined by an otolaryngologist before being referred to our department. Fifteen patients had undergone at least one surgical procedure, including placement of a middle ear tube, sinus surgery, tonsillectomy or adenoidectomy.

Table I: Clinical Characteristics of Patients with Recurrent Infections (n = 61)

Mean age ± SD (yr)	3.8 ± 2.0	
Range (yr)	1-7	
Sex		
Male	43 (70.4%)	
Female	18 (29.5%)	
Infections	Patients (n)	(%)
– Recurrent otitis*	14	22.9
– Recurrent upper respiratory infections**	25	40.9
– Recurrent pneumonia**	12	19.6
– Recurrent otitis with pneumonia*	7	11.4
– Bronchiectasia with sinopulmonary infection	3	4.9
Patients;		
– Non-atopic	29 (47.5%)	
– Atopic	32 (52.4%)	

* at least four episodes in a year.
** at least three episodes in a year.

Immunologic Studies: Serum total IgG, IgA and IgM levels were measured using an auto-analyzer fluoronephelometer (Technicon Instruments Corp., Tarrytown, N.Y.). Serum total IgE levels were measured using Phadebas IgE Prist kit (Pharmacia Diagnostics, Uppsala, Sweden). Serm IgG-subclass levels were determined by radial immunodiffusion technique (The Binding Site Limited^{R}-UK). If the serum IgG-subclass levels were greater than two standard deviations below the mean value of normal, healthy, age-matched controls (Table II), it was considered IgG-subclass deficiency. None of our patients had total absence of any immunoglobulin (Table III).

Table II: Serum IgG Subclass Levels (mg/dL) in Normal Healthy Children (Mean and Ranges)

Age (Year)	n	IgG1	IgG2	IgG3	IgG4
1-2	12	510 (280-890)	140 (30-330)	45 (18-80)	22 (1-65)
3-4	13	605 (385-890)	190 (70-445)	58 (17-95)	7 (0-20)
5-6	25	695 (390-840)	210 (80-515)	64 (8-110)	5 (0-12)
7-8	23	710 (400-895)	275 (110-485)	80 (15-135)	4 (0-7)

Table IIIa: Serum Immunoglobulin and IgG Subclass Levels in Children with Recurrent Respiratory Infections

			Serum Immunoglobulin Levels (mg/dL)							
Patients	Age (Year)	Sex	IgG	IgA	IgM	IgE (iu/mL)	IgG1	IgG2	IgG3	IgG4
1-O.G.	4	F	1130	42	243[a]	15	530	UD	305	47
2-S.C.	2	M	990	45	79	9	750	UD	485	> 1[b]
3-E.Y.	2.5	M	963	48	87	8	670	90	62	> 1[b]
4-E.Y.	2	F	3170[a]	444[a]	275[a]	104	1100	UD	115	33
5-H.T.	7	F	900	41	89	12	660	120	242	UD
6-I.K.	7	M	1615[a]	51	90	23	600	190	40	UD
7-E.B.	7	M	1062	165	96	42	1230	UD	1700	> 1[b]
8-C.A.	2	M	1070	48	243[a]	13	1230	UD	1820	> 1[b]
9-M.G.	7	M	1740[a]	135	147	300[a]	530	300	85	45
10-E.K.	3	M	1250	126	243[a]	76	8360	UD	789	50
11-A.C.Y.	1.5	M	892	86	126	51	5130	90	28	> 1[b]
12-E.D.	7	M	1051	134	204	155	440	250	45	30
13-U.S.	6	M	713	61	143	200	320	UD	24	35
14-Y.K.	7	M	1970[a]	163	192	300[a]	431	UD	23	40
15-M.A.A.	1	M	822	5[b]	121	42	300	100	30	UD
16-E.B.	1	M	570	4[b]	149	5	325	90	22	UD
17-A.K.	1	M	707	4[b]	163	77	1670	90	886	30
18-O.B.	1	M	680	105	20[b]	29	800	450	100	25
19-G.A.	7	M	878	59	51	324[a]	520	900	30	4
20-O.U.	5	F	912	112	125	17	325	200	28	40
21-G.N.	7	F	1234	105	176	56	430	UD	25	20
22-S.K.	2.5	F	1140	UD	220	10	640	250	40	50
23-Z.S.	5	F	2370[a]	135	120	54	648	300	85	45
24-Y.K.	3	M	2974[a]	61	178	78	1100	230	242	41
25-A.A.	3	M	1175	75	105	67	500	200	90	> 1[b]
26-E.C.G.	4	F	1194	153	152	533[a]	600	200	29	22
27-B.A.	5	M	978	80	115	69	450	250	40	30
28-F.S.	7	M	785	97	98	77	600	180	35	18
29-I.G.	3	M	1100	85	89	89	450	200	25	35
30-Y.D.	6	F	980	124	90	15	325	290	45	35
31-B.B.	5	M	890	125	77	78	449	700	30	7
32-N.G.	7	F	1450	76	123	82	740	700	35	21

Table IIIb: Serum Immunoglobulin and IgG Subclass Levels in Children with Recurrent Respiratory Infections

Patients	Age (Year)	Sex	Serum Immunoglobulin Levels (mg/dL)							
			IgG	IgA	IgM	IgE (iu/mL)	IgG1	IgG2	IgG3	IgG4
33-G.N.	5	F	1256	90	99	91	630	650	25	45
34-S.U.	7	M	975	210	129	76	450	550	28	37
35-H.G.K.	7	M	750	86	187	56	538	510	39	18
36-H.Y.	4	M	880	95	145	34	500	UD	38	26
37-O.G.	5	M	1245	167	134	45	460	130	26	8
38-B.S.	1	F	690	179	185	34	890	95	24	12
39-S.N.S.	4	F	895	87	132	21	412	75	21	17
40-B.S.	1	M	1259	162	103	132	825	UD	770	13
41-E.K.	4	F	1338	167	215	171	1060	126	101	11
42-K.A.	2.5	M	1139	99	114	305[a]	1400	241	166	57
43-O.C.	4	F	1376	119	170	131	1100	116	79	43
44-A.S.	4	M	2582[a]	120	128	112	797	129	20	39
45-G.G.	4	M	1497	1497[a]	390[a]	317[a]	1030	204	79	20
46-B.S.	5	M	1024	74	87	42	715	9	48	19
47-S.K.	3.5	M	1704[a]	132	188	284	812	116	37	7
48-H.O.	1.5	M	965	68	127	143	763	116	166	3
49-S.O.	2	F	2340[a]	300[a]	128	1005[a]	1450	241	114	33
50-G.K.	1	F	1138	50	65	2160[a]	513	67	79	3
51-A.E.V.	2	M	605	10	116	68	4210	UD	204	58
52-Y.E.S.	4	M	1336	199[a]	169	494[a]	1100	676	79	72
53-Y.S.E.	3.5	M	2974[a]	67	162	85	1100	UD	242	UD
54-E.I.	3	M	590	50	68	17	513	67	63	1
55-B.A.	1	M	924	63	98	40	450	250	40	30
56-T.K.	2	F	972	152	95	258[a]	1050	576	70	51
57-K.G.	3.5	M	1028	143	204	111	715	150	60	42
58-K.G.K.	4.5	M	986	64	97	35	512	UD	48	61
59-M.K.A.	4	M	1135	145	192	70	875	UD	85	35
60-Y.K.	2.5	M	455	24	110	90	812	144	77	42
61-S.S.K.	3.5	M	1779[a]	95	123	38	585	UD	62	60

a: Ig levels were more than 2 SD above the mean value of the age-matched controls.
b: Ig levels were more than 2 SD below the mean value of the age-matched controls.
UD: Undetectable.

Results

IgA deficiency was determined in four patients (6.5%), and the total IgG level was found low in one patient (1.6%) who had recurrent pneumonia and bronchiectasia. The overall frequency of IgG-subclass deficiency was found to be 39.3 percent (24 patients).

IgG, IgA, IgM and IgE levels were normal in 35 patients. In this group, the frequency of IgG-subclass deficiency was 37.1 percent (13 patients). Selective IgG2 deficiency was detected in seven patients, selective IgG4 deficiency in four patients, and combined IgG2-IgG4 deficiency in two patients (Table IV). In patients who had selective IgA deficiency, we found selective IgG2 deficiency in one patient and selective IgG4 deficiency in one patient.

Table IV: The Frequency of IgG Subclass Deficiency in Patients with Normal and Abnormal Immunoglobulin Levels

	Patients (n = 39)		
	with Normal Ig Levels* (n = 35)	with Normal Ig Levels** (n = 26)	Total (n = 61)
IgG2 deficiency	7	5	12
IgG4 deficiency	4	4	8
IgG2-IgG4 deficiency	2	2	4
Total	9	8	24
(%)	(37.1%)	(42.3%)	(39.3%)

* Ig levels were normal the mean values of the age matched controls.
** Ig levels were more than 2 SD below or above the mean values of the age-matched controls.

An increased serum IgM level was found in three patients, including one patient with IgG2 deficiency and one with combined IgG2-IgG4 deficiency. An increased serum IgG level was found in six patients, including two patients with IgG4 deficiency, one with IgG2 deficiency and one with combined IgG2-IgG4 deficiency. An increased IgE level was found in five patients, including one patient who had selective IgG4 deficiency. The other major immunoglobulin abnormalities are shown in Table V. In addition, the frequency of IgG-subclass deficiency was found to be 31.2 percent (10 of 32 patients) among atopic patients with recurrent infections.

Table V: Distributions of Patients Who Had Abnormal Ig Levels Associated with IgG-Subclass Deficiency

Major Ig Abnormalities*	n	IgG2 Deficiency	IgG4 Deficiency	IgG2-IgG4 Deficiency
Increased IgM	3	1	–	1
Increased IgG	6	1	2	1
Increased IgE	5	–	1	–
Increased IgG, IgE	3	–	–	–
Increased IgA, IgE	1	–	–	–
Increased IgA, IgG, IgE	1	–	–	–
Increased IgA, IgG, IgM	1	–	–	–
Increased IgA, IgM, IgG	1	1	–	–
IgA Deficiency	1	1	–	–
Low IgA Level**	3	–	1	–
Low IgM level	1	–	–	–

* Ig levels were more than 2 SD below or above the mean values of the age-matched controls.
** Partial IgA deficiency.

Discussion

Human IgG immunoglobulins are divided into four subclasses: IgG1, IgG2, IgG3 and IgG4. Recent improvements in measuring IgG subclasses have led to numerous reports of patients with recurrent infections[10, 14-16]. The association between IgG subclass deficiency and recurrent pyogenic infections was first reported by Schur et al.[10] in 1970. The actual incidence of IgG-subclass deficiency is unknown, especially in pediatric patients. Shackelford et al.[11] reported low IgG2 concentrations in seven of 30 children with recurrent infections. In their patient group, immunologic abnormalities were heterogenous, as in our patients. They reported isolated IgG2 deficiency in two patients, combined IgG2-IgG4 deficiency in two patients, IgG2-IgG4-IgA deficiency in one, IgG2-IgGA deficiency in one and severe IgG1-IgG2 deficiency in one patient. Gross et al.[12] reported the incidence of IgG-subclass or major immunoglobulin isotype deficiency as 58 percent in a highly selected population. Twenty-six of 267 patients with recurrent infection had partial IgG-subclass deficiency. Moss et al.[13] reported that isolated IgG4 deficiency had a significantly higher prevalence among patients with recurrent infections (17%). However, they found the prevalence of isolated IgG4 deficiency to be only seven percent among atopic patients. In our study, we found isolated IgG4 deficiency in four of 35 patients (11.4%) with recurrent infections. In addition, we found both IgG4 deficiency and major immunoglobulin abnormalities in four of 26 patients (15.3%). Nevertheless, IgG4 levels could not be detected in 20 percent of normal healthy children by RIA method[19]. Berkel et al.[20] also reported that IgG4 levels had a non-homogenous distribution in Turkish children. Tezcan et al.[17, 18] found IgG-subclass deficiency in five of 11 symptomatic IgA-deficient patients and in two of 12 patients (16.6%) with recurrent infections.

DeBaets et al.[6] studied the incidence of IgG subclass deficiency in 53 children with recurrent bronchitis. They reported the incidence of IgG-subclass deficiency to be 57 percent. In their study, nine patients (17%) were deficient for IgG2, nine (17%) for IgG3, and 20 (38%) for IgG4. None of their patients had IgG1 deficiency, as in our study. We found 12 patients (19.6%) were deficient for IgG2, eight (13.1%) for IgG4 and four (6.5%) for combined IgG2-IgG4. In the children with IgG2 deficiency, Umetsu et al.[15] reported that serum antibody concentrations to the capsular polysaccharide of Haemophilus influenzae type B (Hib) were significantly lower than those in age-matched controls, both before and after immunization with the Hib capsular polysaccharide antigen. Also, IgG2 may be present in normal amounts but non-functional. Thus, serum antibody titers to the tetanus and diphtheria toxoid proteins and Hib capsular polysaccharide antigens should be evaluated in children with recurrent infections[1, 12, 21].

On the basis of these observations, we recommend the evaluation of IgG-subclasses in patients with recurrent infections, whether or not major immunoglobulin abnormalities are present. On the other hand, we suggest that IgG-subclass deficiencies also be evaluated, especially in atopic patients with recurrent infections.

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