IgG subclass levels in patients with Down's syndrome

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Patients with Down Syndrome are predisposed to infectious diseases. In the present study, serum immunoglobulin G subclass levels were determined in (age range from 0.5 to 11.5 years) 20 children with Down syndrome (6 girls, 14 boys) and in 20 healthy children of the same age group, by radial immunodiffusion technique. The mean IgG\ and IgGz levels were increased, while that of IgG was decreased significantly in the patient group, compared to the healthy children. Although the mean IgGz level was found to be lower in Down syndrome group, this difference was not significant statistically. When the patient and control groups were studied in two age groups including subjects under six and above six years; IgGi and IgGz levels were determined to be higher, whereas that of IgG4* to be *lower in both groups of Down syndrome, compared to the same age groups of healthy children. The mean IgGz level was found to be lower in patients under six years, while it did not differ significantly in the group above six years, when compared to the controls. We concluded that, IgG subclass levels have to be determined in children with Down syndrome, in order to evaluate these patients for the risk of infectious diseases. [Turk J Med Res 1996; 14(1): 19-22]*

Key Words: Down's syndrome, IgG subclass deficiency

Tendency to infections is a well known feature of Down's syndrome. Respiratory and gastrointestinal system infections are frequently seen in these patients and they mostly die of these infections (1). Patients with Down's syndrome are in high risk group for leukemia and other malignant disorders and autoimmune diseases (2,3). These findings suggest that an immune system disorder may exist in Down syndrome. The nature of immune defects is not well understood, but abnormalities in cellular immunity (4-6), inflammatory reaction responses (7), interferon production (8), and neutrophil, monocyte and lymphocyte chemotaxis (9-11) were demonstrated in some reports.

Recent studies suggest that IgG subclass deficiency plays role in frequent infections on patients with Down syndrome (12,13).

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In this study, we aimed to evaluate the serum IgG subclass levels in children with Down syndrome.

MATERIALS AND METHODS

We investigated twenty patients (6 girls, 14 boys) who were cytogenetically diagnosed for Down syndrome. Ages of patients change from six months old to 11.5 years. The mean age was 5±3.6 years. Twenty healthy children of the same age group served as controls.

Serum samples obtained from both groups were stored at —20°C. Total IgG, IgA, IgM and IgD levels in the sera were measured with SERA—PAK*, by using immunoturbidimetric method and fluoronephelometre autoanalyser (Technicon Instruments Corp., Tarrytown, N.Y). IgG subclass (IgGi, IgG2, IgG3, IgG4) levels in the sera were tested by radial immunodiffusion method by using commercial kits (U.K Corp. The Binding Side). This method is based upon the relationship between the antigen concentration and the square of the ring diameter during diffusion. By measuring the diameter of the ring produced by that sample and reading off the curve (14).

Results were compared with the levels of healthy Turkish children published previously (15,16).

Statistical evaluation was performed by using Mann Whitney U and Student's t tests.

RESULTS

Values of IgG and IgG subclasses in the patients are shown in Table 1, and the geometrical means of IgG subclasses in the patient and control groups are shown in Table 2.

Serum IgG levels in the patients group were found to be higher than those of the control group ($p<0.01$). There were no significant differences between IgA, IgM and IgD levels ($p>0.05$). None of the patients were found to have decreased total IgG levels in the sera.

The mean serum IgG_1 and IgG_3 levels of the patients were higher than those of the controls ($p<0.01$) whereas the mean serum IgG_4 and IgG_2 levels of the patients were lower ($p<0.01$, $p<0.05$).

Table 1. Serum IgG and IgG subclass values of children with Down's syndrome (mg/dl).

No	Age	Sex	IgG	IgG1	igG2	igG3	igG4
1	8.5	M	1070	883	138	110	27.7
2*	11.5	M	1316	1230	80[b]	50.9	1.7
3	11.5	M	1375	1250	116	155	8.5
4*	8.5	F	1376	1850[a]	254	360[c]	1.9
5	9	F	1170	821	96	77	UD
6	7.5	M	1150	1230	114	328[c]	3.6
7	6.5	F	1050	789	147	148	13.6
8*	8.5	M	1426	1960[a]	204	174	1.3
9	7	M	980	1030	45[b]	85.7	UD
10	2	M	1050	857	37	50.9	UD
11*	1	M	980	883[a]	20[b]	61	6.2
12	5	F	875	1190	158	141	UD
13	2.5	M	1099	657	67.6	68.9	UD
14	2	M	1050	1060	67.6	155[c]	UD
15	2	M	1010	825	86.4	120	1.3
16	0.5	M	850	715	86.1	91.7	1.9
17*	1	M	1072	621	36	127	UD
18	1.5	F	890	769	51	148[c]	UD
19	5	M	1170	1030	147	77	6.9
20	5.5	F	970	1160	228	58.3	1.9

* Patients with recurrent infections
[a]: IgG1 levels were more than 3 SD above the mean value of the healthy children
[b]: IgG2 levels were more than 3 SD below the mean value of the healthy children
[c]: IgG3 levels were more than 3 SD above the mean value of the healthy children
UD: Undetectable

Table 2. The geometrical means of serum IgG subclass levels (Geometrical mean and ±3 SD)

	0-6 age		7-11 age	
(mg/dl)	Down Syndrome (n=11)	Control (n=11)	Down Syndrome (n-9)	Control (n=9)
IgGi	867** (435—3123)	687 (329—1432)	1164** (435—3123)	800 (112—1472)
IgG_2	71.4 (8.3—616)	105.4 (36.2—308)	118.5** (25.6—550)	206 (90.9-467)
IgG_3	92.4* (26.6—320)	62.5 (21.8—179)	137* (19.4—967)	76.9 (19.2—308)
IgG_4	1.618±2.54* (0.178—14.6)	9.14±18 (0.154—540)	3.3U9.13* (0.085—128)	14.15±24.9 (0.175—1141)

Compared to patients group and control group $p<0.05$
Compared to patients group and control group $p<0.01$

When the patients and controls were evaluated in two groups as below six years, the geometrical mean serum IgGi and IgG3 levels of the patients were found to be higher and the geometrical mean IgG4 levels to be lower than those of the controls, in both groups (Table 2).In the patients above six years, the geometrical mean serum IgG2 levels were lower ($p<0.05$), however patients below six years showed no significant difference compared to the controls ($p>0.05$).

DISCUSSION

In the recent years, IgG subclass deficiency has been included among the differential diagnosis of the recurrent infections of children. However, there is still a controversy about the definition of IgG subclass deficiency in literature. In some studies, values below-2 SD of geometrical means of the normal levels for a particular age are defined to be lower (12,13,17).

In the scope of this definition it can be estimated that IgG subclass deficiency has to be seen in 2.5 % of healthy inviduals; and the mean IgG subclass levels determined to be below -3 SD of healthy subjects in different age groups, have to be accepted as IgG subclass deficiencies (15).

In these study we compared IgGi, G_2 and G_3 subclass levels in Down Syndrome group, with the normal levels of healthy Turkish children defined by Berkel et al (16) according to ± 3SD of geometrical means of IgG subclass concentrations. IgGi levels were increased in three patients, IgG2 levels were decreased in three patients and IgG3 levels were increased in four patients. In Berkel's study it was found that serum IgG4 levels were in wide distribution in childhood. For this reason they had not defined the normal ranges of IgG4 levels in healthy children.

On the other hand, Keller and Stanvord reported that though the IgG4 concentrations are 1-3% of serum total IgG, it may have a unique role in mucosal defense because of its higher relative concentrations in secretions (18-20), its inability to activate complement, to bind to Fc receptors of phagocytic cells notwithstanding (21). Heiner et al (22) have noted the causal relationship between IgG4 deficiency and predilection to infections especially of respiratory tract. It should be considered that 10-25 % of general populations have IgG4 concentrations that can not be detected with immunodiffusion methods (23) in the diagnosis of IgG4 deficiency. The serum IgG4 levels were undetectable in 3 (15%) healthy children in our study.

Loh et al (13) reported that IgG4 deficiency was diagnosed in 14 (54%) children while IgG2 deficiency in one child. However none of the children with Down syndrome had deficiency of total IgG.

in our study, serum IgG4 levels were undetectable in eight (40 %) patients. One of these patients was seven years old, the other nine and all the others were younger than five years. Total IgG levels of these patients were normal.

Children with Down syndrome are especially prone to respiratory bacterial infections (24). It is not exactly known why a deficiency of IgG4 should lead to a reduction in host defense against infections. This may be explained by a deficiency in IgG2 and IgG4 antibodies, of which the former are known to be directed primarily against bacterial polysaccharide antigens of encapsulated bacteria, such as Streptococcus pneumonia and Hemophilus influenza (12).

IgG2 deficiency tends to develop later in life among children and adults with Down syndrome (12). In our study, the mean serum IgG2 level in the patient group above six years was found to be lower than the control group. This result shows that IgG4 deficiency plays role in early ages, but IgG4 and IgG2 deficiencies play role together in the later ages of children with Down syndrome, thus prone to infections.

In this study, the mean serum IgGi and IgG3 levels in the children with Down syndrome were found to be higher than control group. This finding is similar to study of Anneren et al (12). it was suggested that the higher serum concentrations of IgGi and IgG3 in the children with Down syndrome compared with the controls may well be a consequence of polyclonal stimulation from repeated bacterial infections (12).

Six of our patients with Down syndrome (2,4,6,8,11,17 th. patients) had recurrent infections of upper and lower respiratory tract. Three patients having increased IgGi levels, two of three patients with increased IgG3 levels and two of six patients with undetectable level of IgG4 had history of recurrent infections.

These results show that from the point of recurrent infections in patient with Down syndrome, the increased level of IgGi is of more importance, and decreased level of IgGi is of more importance, and decreasedlevel of IgG2 and increased level of IgG3 may not appear with recurrent infections and also decreased level of IgG4 may not be related to infections.

The reasons of the abnormal serum IgG subclass pattern in children with Down syndrome is not clear. Anneren et al (12,25) reported that this abnormality is probably due to secondary effects of either a factor related to immunoglobulin production of deficiency of a trace element such as selenium. These results suggest that, it is important to determine IgG subclasses and emphasize that a normal serum IgG concentration does not exclude the possibility of an IgG subclass deficiency.

We conclude that, IgG subclass levels have to be determined in children with Down syndrome in order to evaluate these patients for the risk of infectious diseases.

Down sendromlu hastalarda
IgG subgrup düzeyleri

*Enfeksiyonlara yatkınlık Down sendromunun bilinen bir özelliğidir. Bu çalışmada 0.5-11.5 yaşları arasında 6'sı kız, 14'ü erkek 20 Down sendromlu çocuk ve aynı yaş grubundaki sağlıklı 20 çocukta serum immunglobulin G subgrup düzeyleri ölçüldü. Down sendromlu çocukların ortalama serum IgGı ve IgG **3** düzeyleri kontrol grubuna göre yüksek bulunurken, serum IgG **2** ve IgG* düzeyleri önemli derecede düşük bulundu. Down sendromlu hastalar ve kontrol grubu 6 yaştan küçük ve büyük olmak üzere iki gruba ayrılarak incelendiğinde; her iki hasta grubunda da ortalama serum* /g/Gı *ve IgGz düzeyi ise daha düşük bulundu. Serum ortalama IgGz düzeyleri 6 yaştan büyük hasta grubunda kontrollere göre daha düşük bulunurken, 6 yaştan küçük hasta grubunda ise kontrol grubuna göre önemli bir farklılık göstermedi. Bu sonuçlar; Down sendromlu çocukların değerlendirilmesi sırasında enfeksiyon riski açısından serum IgG subgruplarının belirlenmesinin önemine dikkat çekmektedir. [Turk JMed Res 1996; 14(1): 19-22]*

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