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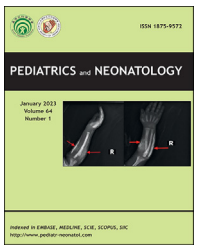

Original Article

Clinical and laboratory evaluation of Turkish children with IgG subclass deficiency

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Key Words
antibody deficiency;
child;
IgG subclass deficiency

Background: IgG subclass deficiency is a laboratory diagnosis and becomes important with recurrent infections. This study aimed to examine the demographic, clinical, and laboratory results of pediatric cases with IgG subclass deficiency and to improve the understanding of the clinical significance of IgG subclass deficiency.
Methods: In this study, the clinical and laboratory features of 111 pediatric patients, with at least one whose serum IgG subclasses was measured as lower than 2 standard deviation of healthy aged-matched control values, were evaluated. The clinical and laboratory features of the cases with isolated IgG subclass deficiency (Group 1) and those with low serum levels of any of IgG, IgA, and IgM in addition to the IgG subclass deficiency (Group 2) were compared.
Results: A total of 55 (49.54%) and 56 (50.45%) patients were included in Groups 1 and 2, respectively. Among our studied cases, 20 (18.1%) had a history of hospitalization in the neonatal period, 61 (54.95%) had at least one hospitalization due to infection, and 55 (49.54%) had a history of recurrent infection. The frequencies of these three conditions were statistically significantly higher in Group 2 ($p < 0.05$). The frequencies of infections in the last year in Groups 1 and 2 were 4.4 ± 1.2 and 5.4 ± 1.9, respectively ($p < 0.05$). As a result of recurrent infections, 43.24% ($n = 48$) of our patients received antibiotic prophylaxis, and 21.62% ($n = 24$) had immunoglobulin replacement therapy. Furthermore, the numbers of patients who needed these treatments were higher in Group 2 ($p < 0.05$).
Conclusion: In cases with IgG subclass deficiencies, concomitant main-group immunoglobulin deficiencies may increase the number and severity of infections, leading to hospitalizations,

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antibiotic prophylaxis, and immunoglobulin therapy. More attention should be paid to cases of immunoglobulin main-group deficiencies in the follow-up of these cases.

1. Introduction

Primary immunodeficiencies (PIDs), also called inborn error of immunity, include a group of more than 400 inherited diseases usually caused by single-gene mutations and result in specific impairments in normal immune development and function.[1] Primary antibody deficiencies (PADs) account for about half of PIDs and are the most common PIDs. PADs represent a wide group of diseases, from diseases with severe decreases in all serum Ig levels and the absence of B cells to diseases with selective antibody deficiency with normal serum Ig levels. The early diagnosis and adequate treatment of PADs are the keys to survival and a better quality of life of patients. Delays in diagnosis and/or inadequate treatment may result in permanent organ damage (e.g., bronchiectasis or bronchiolitis obliterans) or death from severe infections.[2]

IgG subclass deficiency, an antibody deficiency, was first described in 1970 in three patients by Schur et al.[3] IgG subclass deficiencies have been described in a large number of pediatric patients over the years.[4] IgG subclass deficiency is a condition in which one or more IgG subclass serum levels are 2 standard deviations (SDs) below the normal levels for age in a patient with a normal total IgG amount.[5] As most of these patients are asymptomatic, this condition is considered as a laboratory result rather than a disease. A clinically significant diagnosis of IgG subclass deficiency involves an impaired functional antibody response with recurrent infections.[6] IgG subclass deficiencies can be asymptomatic or present with recurrent infections or accompany another PID. Respiratory tract infections are the most common result in symptomatic patients. The frequency and severity of these infections are variable. They are often associated with common respiratory pathogens causing otitis, sinusitis, and pneumonia.[7]

This retrospective study aimed to evaluate the clinical and laboratory results of 111 pediatric patients diagnosed with IgG subclass deficiency to reveal their relationship with other comorbidities and the need for treatment. Thus, this research will contribute to a better understanding of the clinical significance of IgG subclass deficiency as a laboratory result.

2. Materials and methods

Patients who applied to Necmettin Erbakan University Meram Medical Faculty Pediatric Allergy and Immunology outpatient clinic between January 2006 and October 2021 and diagnosed with IgG subclass deficiency by measuring at least one of serum IgG subclasses as 2 SD below the required value were included in this study. The clinical and laboratory findings of 111 cases, aged between 2 and 18 years, were evaluated retrospectively.

The demographic data of patients, such as age and gender, age at diagnosis, consanguinity between parents, family history of immunodeficiency, hospitalization in the neonatal period, need for mechanical ventilation in the neonatal period, history of hospitalization, frequency of infection in the last 1 year, comorbidities, antibiotic prophylaxis, and intravenous immunoglobulin treatment status, were recorded. More than eight upper respiratory tract infections, more than two sinus infections, and/or more than two lower respiratory tract infections in a year were considered as recurrent respiratory tract infections. In our study, patients with recurrent infections were given antibiotic prophylaxis. Immunoglobulin replacement therapy (IgRT) was used in IgG-subgroup-deficiency patients with recurrent infections if the accompanying specific antibody response was impaired, if the patient showed no response to antibiotic prophylaxis, or if a concomitant functional immunoglobulin deficiency was observed. Patient data were collected using hospital files and records in pediatric immunology cards.

Nephelometrically measured IgA, IgM, IgG, and IgE serum values and IgG subclass (IgG1, IgG2, IgG3, and IgG4) levels were recorded. As normal reference values for age, the results of the study of Aksu et al.[8] on more than 500 healthy Turkish children were accepted as reference. Isohemagglutinin titers were interpreted as low if the anti-A and anti-B titers, which were detected in the blood bank of our hospital in accordance with standard methods, were below 1/8. If the hepatitis-B antibody response was below 10 mIU/mL, the tetanus antibody response was below 0.1 IU/mL, and if the pneumococcal antibody response was below 3500 mU/mL according to the reference range of our hospital, it was interpreted as an inadequate pneumococcal antibody response.[9] Peripheral blood lymphocyte subgroup analysis values were recorded. For the peripheral blood lymphocyte subgroup evaluation, the result of the study by İkincioğulları et al.[10] was used as a reference.

None of the cases had diseases that cause secondary immunoglobulin losses, such as protein-losing enteropathy, nephrotic syndrome, and lymphoproliferative disease.

Allergic diseases were classified as asthma, allergic rhinitis, atopic dermatitis, pollen allergy, house dust allergy, and food allergy. The Global Initiative for Asthma guideline[11] was used for the diagnosis of asthma. The diagnosis of allergic rhinitis was performed in accordance with the study of Bousquet et al.[12] The diagnosis of atopic dermatitis was conducted in accordance with the criteria of Hanifin and Rajka.[13] Pollen and house dust allergies were evaluated based on the results of the skin prick test.

2.1. Statistical analyses

All data were analyzed in a computer environment using SPSS 25.0 package program. Descriptive statistics were expressed as numbers and percentages. Categorical data

were compared using the Chi-square test. Fisher's exact test was used when the expected value was less than 5 in more than 20% cells in multi-span tables. Normally distributed values were given as "mean ± SD." Non-normal distribution values included the median 25th and 75th percentiles. In the analysis of continuous variables with normal distribution, t test was used in independent groups, and the Mann–Whitney U test was applied in the analysis of the two groups and in continuous variables that did not show normal distributions. The statistical significance level in the study was accepted as $p < 0.05$.

2.2. Ethical approval

The study was approved by the Necmettin Erbakan University Meram Medical Faculty Clinical Research Ethics Committee (approval number: 2021/3493). Informed consent was waived due to the retrospective design of the study.

3. Results

A total of 111 cases diagnosed with IgG subclass deficiency were included in the study. Isolated IgG subclass deficiency was diagnosed in 55 (49.54%) of the cases (Group 1), and 56 had a main immunoglobulin (IgG, IgA, and IgM) deficiency (Group 2) accompanying IgG subclass deficiency.

In our study, 68 (61.26%) of the cases were male, and 43 (38.73%) were female. The IgG subclass deficiency was higher in males ($p < 0.05$). The mean age at diagnosis was 88.5 ± 49 months. A total of 20 (18.01%) cases had a history of neonatal hospitalization, 61 (54.95%) had at least one hospitalization due to infection, and 55 (49.54%) had recurrent respiratory tract infections. The frequencies of these three conditions were statistically significantly higher in Group 2 ($p < 0.05$). Antibiotic prophylaxis was given to 48 (43.24%) patients, and IgRT was applied to 24 (21.62%) patients due to recurrent infections. The numbers of patients who needed these treatments were higher in Group 2 ($p < 0.05$). Allergic disease was found in 41 (37.27%) of our patients with IgG subclass deficiency, and asthma was found in 23 (20.7%). No significant difference was observed between Groups 1 and 2 in terms of asthma and allergic diseases. Two patients with isolated IgG subclass deficiencies had bronchiectasis, and one had bronchiolitis obliterans. Table 1 shows the demographic and clinical features of the cases with IgG subgroup deficiency, and Table 2 provides the immunoglobulin values.

IgG3 deficiency was the most common type of IgG subclass deficiency in our cases (76.57%, n = 85). A total of 16 patients (14.41%) showed a high IgE level, and no difference was observed between the two groups ($p > 0.05$). Hepatitis-B vaccine response was evaluated in 95 (85.58%) cases. Exactly 79 patiens (83.16%) had a normal post-vaccination hepatitis-B vaccine response. The pneumococcal vaccine response was evaluated in 71 (63.96%) cases. Among these 71 patients, 25 (35.21%) had a normal pneumococcal vaccine response. The tetanus vaccine response was recorded in 80 (72.07%) patients. A normal tetanus vaccine response was detected in 43 (53.75%) of these cases. No significant difference was observed between Groups 1 and 2 in terms of tetanus-, pneumococcus-, and hepatitis-B-specific vaccine responses. The isohemagglutinin response was evaluated in 91 (81.98%) cases, and it was normal in 79 (86.81%) cases. One patient had a low isohemagglutinin response in Group 1, and the other patients with a low isohemagglutinin response were observed in Group 2 ($p < 0.05$). When IgG subclass deficiencies were compared with peripheral lymphocyte subgroup values, no significant relationship was found between them ($p > 0.05$). Peripheral lymphocyte subclasses were examined in 67.27% (n = 37) of our cases in Group 1, and switched-memory B lymphocytes (CD27) and recent thymic emigrants (CD31) were examined in 47.27% (n = 26). Peripheral lymphocyte subclass was measured in 92.85% (n = 52) of the patients in Group 2, CD27 levels were measured in 69.64% (n = 39), and CD31 levels were evaluated in 67.85% (n = 38) of the patients. No significant difference was observed between the two groups in terms of peripheral lymphocyte subgroups, CD27, and CD31 ratios (Table 3).

Our cases with IgG subclass deficiency were compared in terms of peripheral lymphocyte subclass levels and absolute values. The mean CD19 lymphocyte ratio of 24 patients with normal IgG1 level was 12.6% ± 6.6%, and that of 65 patients with low IgG1 level was 18.5% ± 7.1%. The mean lymphocyte ratios of patients with low IgG1 levels were significantly higher ($p < 0.05$). However, when the peripheral lymphocyte subclass absolute values of both groups were compared, no significant difference was observed ($p > 0.05$).

Both groups were compared in terms of tonsillopharyngitis, otitis media, sinusitis, lower respiratory tract infections, urinary infections, and gastrointestinal infections. The number of patients with a lower respiratory tract infection was significantly higher in Group 2 ($p < 0.05$). No significant difference was observed between the two groups in terms of tonsillopharyngitis, otitis media, sinusitis, urinary infections, and gastrointestinal infections ($p > 0.05$).

A total of 45 patients included in the study had regular follow-ups, and the mean and median follow-up durations were 45 and 29 months, respectively. No recovery was observed in any IgG subgroup in 66.67% (n = 30) of the 45 patients. The improvement with age was observed in 15 patients (33.33%). IgG1 levels improved with age in two patients with IgG1 deficiency. Eight patients showed improvement in IgG2, and IgG3 improved in one patient. One patient showed simultaneous improvements in IgG1, IgG2, and IgG4 levels.

4. Discussion

To evaluate IgG subclass deficiency, which is a laboratory diagnosis, scientists should consider the frequency and severity of recurrent infections and the lack of specific antibody responses in patients. In our cases, the frequency of recurrent infections was 49.54%, and the hospitalization rate was 54.95%. These rates differed in terms of isolated IgG subclass deficiency and immunoglobulin deficiency accompanying IgG subclass deficiency. For these reasons, our study is a unique research evaluating these features and

Table 1 The demographic and clinical characteristics of the cases diagnosed with IgG subclass deficiency.

Clinical features	Group 1 (n = 55)	Group 2 (n = 56)	P value
Gender (n, %)			
Male	33 (60.00%)	35 (62.50%)	0.787
Female	22 (40.00%)	21 (37.50%)	
Diagnostic age (month) (mean ± SD)	95.1 ± 54.0	78.7 ± 41.3	0.076
Consanguinity (between parents)			
No (n, %)	51 (92.72%)	49 (87.50%)	0.357
Yes (n, %)	4 (7.27%)	7 (12.50%)	
Family history of immunodeficiency			
No (n, %)	54 (98.18)	53 (94.64)	0.618
Yes (n, %)	1 (1.81)	3 (5.36)	
Hospitalization in the neonatal period			
No (n, %)	51 (92.72)	40 (71.42)	**0.004**
Yes (n, %)	4 (7.27)	16 (28.58)	
Mechanical ventilation in the neonatal period			
No (n, %)	54 (98.18)	49 (87.50)	0.061
Yes (n, %)	1 (1.81)	7 (12.50)	
History of previous hospitalization			
No (n, %)	32 (58.18)	18 (32.14)	**0.006**
Yes (n, %)	23 (41.81)	38 (67.86)	
Frequency of infections (in a year) (mean ± SD)	4.4 ± 1.2	5.4 ± 1.9	**0.002**
Number of hospitalizations (in a year) (median [IQR])	0.0 (1.0)	1.0 (3.0)	**0.004**
Recurrent respiratory infection (n, %)			
Yes	16 (29.10%)	39 (69.64%)	**<0.01**
No	39 (70.90%)	17 (30.36%)	
Antibiotic prophylaxis (n, %)			
Yes	16 (29.10%)	32 (57.14%)	**0.003**
No	39 (70.90%)	24 (42.86%)	
Intravenous ımmunoglobulin (n, %)			
Yes	6 (10.91)	18 (32.14)	**0.021**
No	49 (89.09)	38 (67.86)	
Allergic disease (n, %)			
Yes	20 (36.36)	21 (37.50)	0.844
No	35 (63.64)	35 (62.50)	
Asthma (n, %)			
Yes	11 (20.00)	12 (21.43)	>0.99
No	44 (80.00)	44 (78.57)	

contributes to the literature in terms of understanding the clinical importance of IgG subclass deficiency.

According to the study of Hanson et al.,[14] the male/female ratio associated with IgG subclass deficiency was 3:1. According to the study performed by Karaca et al. on 59 patients with 15 IgG subclass deficiencies in our country, the male/female ratio was 1.38, which is similar to the gender ratio in our study. In our research, the male/female ratio of the cases with IgG subclass deficiency was 1.58, and the condition was more common in males. The effect of gender on IgG subclass deficiency is unknown, and the higher frequency observed in males is common in general.

Consanguinity was observed between the parents of 11 (9.91%) out of the 111 patients included in our study. Although the frequency of consanguineous marriage in our country varies regionally, it reached 24.00% in the 2018 research of the Turkey Demographic and Health Survey.[15] In our study, the frequency of consanguinity was lower than the average in Turkey. Therefore, according to the results of our study, no relationship exists between consanguinity and IgG subclass deficiency. Four patients (3.60%) had a family history of immunodeficiency. One of these patients was in Group 1 and three were in Group 2 ($p > 0.05$). In the study performed by Yorulmaz et al.[16] in our center, none of the 33 patients with isolated IgG subclass deficiency had a family history of immunodeficiency. In this context, no relationship exists between isolated IgG subclass deficiency and a family history of immunodeficiency.

A history of previous hospitalization was recorded in 61 (54.95%) of the patients evaluated in the study. When the two groups were compared in terms of hospitalization, the frequency of hospitalization of cases in Group 2 was statistically significantly higher. A total of 20 patients (18.02%) had a history of hospitalization in the neonatal period, and

Table 2 Laboratory characteristics of cases diagnosed with IgG subclass deficiency.

Immunoglobulins	Group 1	Group 2	P value
IgG (mg/dL)			
IgG at the time of initial diagnosis n, (mean ± SD)	55, (963.7 ± 203.8)	56, (699.7 ± 303.6)	**0,029**
IgG during follow-up n, (median [IQR])	21, (945 [838,5–1130])	37, (646 [540–920])	**< 0,001**
IgA (mg/dL)			
IgA at the time of initial diagnosis n, (median [IQR])	55, (101 [71–163])	56, (47,5 [29,5–85,75])	**< 0,001**
IgA during follow-up n, (mean ± SD)	18 (126,7 ± 36,6)	37 (71,0 ± 43,7)	**< 0,001**
IgM (mg/dL)			
IgM at the time of initial diagnosis n, (median [IQR])	55, (102 [85–127])	56, (64 [49,25–80,50])	**< 0,001**
IgM during follow-up n, (median [IQR])	18, (86,5 [68,75–114,25])	37, (63 [45–79,50])	**< 0,001**
IgG1 (mg/dL)			
Normal for age, n (%)	24 (43.64%)	10 (17.86%)	**0.003**
Low for age, n (%)	31 (56.36%)	46 (82.14%)	
IgG1 at the time of initial diagnosis n, (median [IQR])	55, (649 [465–840])	56, (490 [392,75–664.75])	**0.002**
IgG1 during follow-up n, (median [IQR])	19, (645 [584–846])	31, (446 [362–641])	**0.004**
IgG2 (mg/dL)			
Normal for age, n (%)	47 (85.45%)	39 (69.64%)	0.052
Low for age, n (%)	8 (14.55%)	17 (30.36%)	
IgG2 at the time of initial diagnosis n, (median [IQR])	55, (215 [172–290])	56, (170 [113,25–232])	**0.002**
IgG2 during follow-up n, (median [IQR])	19, (214 [158–297])	31, (183 [136–240])	0.174
IgG3 (mg/dL)			
Normal for age, n (%)	16 (29.09%)	10 (17.86%)	0.146
Low for age, n (%)	39 (70.91%)	46 (82.14%)	
IgG3 at the time of initial diagnosis n, (median [IQR])	55, (29 [18–40])	56, (20 [15,25–28,75])	**0,008**
IgG3 during follow-up n, (median [IQR])	20, (27,5 [19–35,75])	32, (20,5 [14–27])	0.072
IgG4 (mg/dL)			
Normal for age, n (%)	32 (58.18%)	18 (32.14%)	**0.006**
Low for age, n (%)	23 (41.72%)	38 (67.86%)	
IgG4 at the time of initial diagnosis n, (median [IQR])	55, (39 [7,4–67])	56, (13 [6,25–44,25])	0.055
IgG4 during follow-up n, (median [IQR])	19, (19 [6–54])	32, (17 [6–31,50])	0.545

8 (7.21%) needed mechanical ventilation during their neonatal hospitalization. Exactly 16 of the 20 patients hospitalized in the neonatal period were in Group 2. The frequent hospitalization in Group 2 may be due to the low level of at least one of IgG, IgA, and IgM in addition to IgG subclass deficiency. On the other hand, infections progress more severely and cause hospitalization with other accompanying immunoglobulin deficiencies.

Recurrent infections in children are a major cause of morbidity and hospitalization worldwide. Patients with IgG subclass deficiencies may be asymptomatic or present with recurrent infections. According to our study, approximately half of the patients with IgG subclass deficiencies had recurrent respiratory tract infections. Thus, approximately half of the patients with IgG subclass deficiency will be asymptomatic. Recurrent infections were observed in 16 (29.09%) of the 55 patients in Group 1 with isolated IgG subclass deficiency. In Group 2 with accompanying antibody deficiencies, 39 (69.64%) of the 56 patients had recurrent infections. These results support the argument that low immunoglobulin levels accompanying IgG subclass deficiency will increase the frequency of recurrent infections.

Allergic diseases are more common in individuals with IgG subclass deficiency than in the normal population.[14] In our study, the frequency of IgG subclass deficiency accompanying an allergic disease was 36.94%. In a study by Kütükçüler et al.,[17] the frequency of allergic diseases in IgG subclass deficiency cases was 24%, which is lower than that in our study. In another research, the frequency of allergic diseases (40%) was similar to the rate recorded in our study.[18] These results suggest that the frequency of allergic diseases in IgG subclass deficiency increases compared with the rate of allergic diseases in populations. Although patients are evaluated in terms of immunodeficiency, they should also be assessed in terms of allergic disease symptoms.

In our study, 23 (20.72%) patients with IgG subclass deficiency had accompanying asthma. Studies have shown that IgG subclass deficiency is associated with asthma.[19] As a result of studies involving children and adults from different societies all over the world, the prevalence of asthma varies between 1% and 18%.[20] The higher prevalence of asthma than the rate in the general population may be related with insufficient neutralization and/or elimination of allergens in patients with IgG subclass deficiency.

The survival of patients with IgG subclass deficiencies is generally good with appropriate treatment, and the frequency of recurrent infections is reduced significantly.[21] In our study, 43.24% of our cases were given antibiotic prophylaxis due to recurrent infections. In another research, 63.63% of 55 patients with IgG subclass deficiency needed

Table 3 Specific antibody responses and lymphocyte subclasses of our patients with IgG subgroup deficiency.

	Group 1 (n, %)	Group 2 (n, %)	P value
Hepatitis B vaccine response			
Adequate (n, %)	34 (77.27%)	45 (88.24%)	0.155
İnadequate (n, %)	10 (22.73%)	6 (11.76%)	
Pneumococcus vaccine response			
Adequate (n, %)	8 (32.00%)	17 (37.96%)	0.676
İnadequate (n, %)	17 (68.00%)	29 (63.04%)	
Tetanus vaccine response			
Adequate (n, %)	16 (53.33%)	27 (54.00%)	0.954
İnadequate (n, %)	14 (46.67%)	23 (46.00%)	
Isohemagglutinin response			
Normal (n, %)	41 (97.62%)	38 (77.55%)	**0.005**
Low (n, %)	1 (2.38%)	11 (22.45%)	
Lymphopenia			
Yes	0 (0.00%)	3 (5.36%)	0.243
No	55 (100.00%)	53 (94.64%)	
Absolute CD3 (by age)			
Low	0 (0.00%)	4 (7.69%)	0.138
Normal	37 (100.00%)	48 (92.31%)	
Absolute CD4 (by age)			
Low	1 (2.70%)	4 (7.69%)	0.397
Normal	36 (97.30%)	48 (92.31%)	
Absolute CD8 (by age)			
Low	0 (0.00%)	4 (7.69%)	0.138
Normal	37 (100.00%)	48 (92.31%)	
Absolute CD19 (by age)			
Low	4 (10.81%)	5 (9.62%)	>0.99
Normal	33 (89.19%)	47 (90.38%)	
Absolute CD16-56 (by age)			
Low	11 (29.73%)	14 (26.92%)	0.772
Normal	26 (70.27%)	38 (73.08%)	
CD27 rate (by age)			
Low	8 (30.77%)	17 (43.59%)	0.298
Normal	18 (69.23%)	22 (56.41%)	
CD31 rate (by age)			
Low	0 (0.00%)	0 (0.00%)	>0.99
Normal	26 (100.00%)	38 (100.00%)	

antibiotic prophylaxis,[22] and a higher rate of antibiotic prophylaxis was used compared with our study. In the study by Kütükçüler et al.,[17] in which 87 patients with IgA/IgG subclass deficiency were evaluated, 78.16% of the patients were given antibiotic prophylaxis. The higher antibiotic prophylaxis given in this previous study[17] compared with our work may be due to the inclusion of patients with recurrent infections and IgG subclass deficiency in our study. In our study, approximately half (43.24%) of the patients with IgG subclass deficiency needed antibiotic prophylaxis because of recurrent infections. The patients in Group 2 needed higher doses of antibiotic prophylaxis. If IgG subclass deficiency is accompanied by main-group immunoglobulin deficiency (IgG, IgA, and IgM), the need for antibiotic prophylaxis increases.

In our study, 21.62% of all cases were given IgRT. This therapy was given to 6 of the 55 patients in the group with isolated IgG subgroup deficiency (Group 1) and 18 of the 56 patients in Group 2. The patients in Group 2 had a significantly higher need for IgRT. With the review of the literature, 18 of the 55 patients (32.73%) needed IgRT in a study.[22] According to the study of Karaca et al., 15.25% of 59 patients with IgG subclass deficiency needed IgRT. In IgG subclass deficiency, different results can be observed in the literature regarding the need for IgRT given that no definite indications are available for this treatment, and each center has their own approach. Another result in our study regarding IgRT is the increased need for this treatment in Group 2. The need for IgRT might have increased because patients with hypogammaglobulinemia were included in Group 2, and hypogammaglobulinemia increased the frequency and severity of infection in these patients.

Several studies showed that IgG subclass deficiency is associated with chronic lung diseases and bronchiectasis.[14,23,24] In our study, bronchiectasis was found in five patients with IgG subclass deficiency, and bronchiolitis obliterans was detected in two patients. Exactly 2 of the 55 patients with isolated IgG subclass deficiency (Group 1) had

bronchiectasis. These two patients with bronchiectasis had IgG1 and IgG3 deficiencies. In the study by Yorulmaz et al., 7 of the 33 patients with IgG subclass deficiency had chronic lung disease findings, such as fibrotic changes in the lung and peribronchial thickening and bronchiectasis in one patient. In this context, a relationship exists between IgG subclass deficiency and chronic lung diseases. However, further studies are needed for this subject.

Different results were obtained in various studies regarding the frequency of IgG subclass deficiency within itself. In our study, IgG3 deficiency (76.57%) was the most common IgG subclass deficiency. According to the study by Karaca et al.[21] in our country, the most common IgG subclass deficiency was IgG3 deficiency (77.00%). In another study conducted in Thailand, isolated IgG3 deficiency was reported at a rate of 56.40%, and the value was 85.50% with other subclass deficiencies. In a study evaluating 503 patients, including adult patients, with IgG subgroup deficiency, the most common deficiency in children was IgG2 deficiency, and IgG3 deficiency became dominant with age. In the same study, IgG2 deficiency was dominant before the age of 5, and IgG3 deficiency was dominant after the age of 5 years.[25]

In our study, isohemagglutinin titer was measured in 42 cases with isolated IgG subclass deficiency. Isohemagglutinin antibody titer was low in one case (2.38%). Given this result, a low isolated IgG subclass causes no effect on the antibody response to isohemagglutinin. In the group with main immunoglobulin (IgG, IgM, and IgA) deficiencies, isohemagglutinin response was low in 11 (22.45%) of the 49 patients in Group 2. Significantly more patients with a low isohemagglutinin titer were observed in Group 2 ($p < 0.05$). The patients with a low IgM level in Group 2 might have caused this situation. Thus, isohemagglutinin titer must be routinely measured in patients with isolated IgG subclass deficiencies, but such may be more useful when an accompanying reduction of one of the immunoglobulins is observed.

When the relationship between IgG subclass deficiency and peripheral blood lymphocyte subgroups was evaluated, no similar studies were found in the literature. In our study, when the average of peripheral lymphocyte subgroups of patients with low IgG1, IgG2, IgG3, and IgG4 deficiencies were compared, no significant relationship was found. On the other hand, the mean values of CD19+ B lymphocyte ratios of patients with low IgG1 levels were significantly higher and at normal rates compared with patients with normal IgG1 levels. In our study, the mean CD19+ B lymphocyte of patients with low IgG1 was 18.5 ± 7.1, and it was similar to the normal CD19+ lymphocyte ratios in healthy Turkish children.[10] In addition, no significant difference was observed compared with the absolute values of CD19+ B lymphocytes. In our opinion, the higher CD19+ lymphocyte ratio in patients with low IgG1 levels may be due to the immune system increases in the CD19+ lymphocyte ratio because a low IgG1 often causes hypogammaglobulinemia. In the study by Yorulmaz et al., peripheral lymphocyte subgroups were examined in 20 of the 33 patients with IgG subclass deficiency, and the results were normal. More studies are needed to evaluate the relationship between IgG subclass deficiency and peripheral lymphocyte subgroups. We conclude that the routine examination of peripheral lymphocyte subgroups in patients with IgG subclass deficiency is unnecessary.

In conclusion, cases of IgG subclass deficiency in children may progress asymptomatically or present with recurrent sinopulmonary infections. In some patients, these infections may lead to hospitalization. Antibiotic prophylaxis or IgRT may be required because of recurrent infections. The results of our study showed that concomitant main-group immunoglobulin (IgG, IgA, and IgM) deficiencies in cases with IgG subclass deficiency increase the number and severity of infections, cause hospitalizations, and increase the need for antibiotic and IgRT. Thus, the follow-up and treatment of cases with IgG subclass deficiencies must be planned considering these features and evaluated in terms of main-group deficiencies intermittently.

Declaration of competing interest

The authors have declared that they have no conflicts of interest relevant to this article.

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