Allergic diseases in children with primary immunodeficiencies

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The aim of this study was to evaluate and compare the frequency of atopy and allergic disease in all groups of primary immunodeficiency (PID) patients. The study was done on 318 patients with PID between the ages of 6 months and 18 years. The patients and their parents were questioned regarding their histories of asthma and allergic disease. Within the study group, 82.4% of the patients had antibody deficiency, 10.4% combined immunodeficiency, 6.6% phagocyte number or function defect, and 0.6% complement deficiency. Patients with selective immunoglobulin (Ig)A deficiency had a more significant history of ever wheezing compared to those with IgG subclass deficiency (p=0.022). The frequency of current wheezing was higher in patients with antibody deficiency than in patients with combined immunodeficiency (p=0.049). In conclusion, patients with antibody deficiency, especially those with selective IgA deficiency, should be evaluated regarding asthma and allergic diseases if recurring respiratory symptoms are present.

Key words: allergy, antibody deficiency, atopy, primary immunodeficiency.

Primary immunodeficiencies (PID) are rare diseases due to a malfunctioning immune system that is a result of hereditary or spontaneous genetic defects. Advancements in molecular genetics and immunology have brought about an increase in the number of genes responsible for PID, providing a better understanding of the pathophysiology of these diseases[1].

It has long been known that there is a correlation between some PID and allergic diseases. For example, it has been reported that immunodeficiencies like hyper immunoglobulin (Ig)E syndrome and Wiskott-Aldrich syndrome have an atopic component. It has been reported that in some of the other immunodeficiencies, especially those due to antibody deficiencies, atopy is higher than in the general population, but the mechanism behind this is not known[2].

Since patients with PID and allergic disease first present to the clinic with similar complaints, these two disease groups frequently take the same place in their differential diagnosis[3,4]. Most of the studies done on the frequency of atopy and allergic disease in PID patients are limited to antibody deficiencies. In this study, we aimed to evaluate and compare the frequency of atopy and allergic disease in all groups of PID patients.

Material and Methods

Study Design and Population

This study was undertaken in Ankara Children's Health and Diseases Hematology-Oncology Hospital between January 2011 and January 2012 with the approval of the local ethics committee. The study was done on 318 patients with PID between the ages of 6 months and 18 years. The patients and their parents were questioned on their histories of asthma and allergic disease. Skin prick tests were done, and complete blood count and serum IgE levels were measured for all patients. A documented informed consent was obtained from the patients and their parents.

Primary Immunodeficiency

Patients were diagnosed and classified according to the clinical and laboratory criteria of PID reported by the International Union of Immunological Societies (IUIS) Primary Immunodeficiency Diseases Classification Committee[5]. Two types of IgA deficiency may be distinguished: the selective IgA deficiency, with IgA level less than 6 mg/dl, and the partial

IgA deficiency, with a level greater than 6 mg/dl but less than 2 standard deviations below the age-adjusted mean level. Additionally, every diagnosis was grouped into antibody deficiency, combined immunodeficiency, phagocyte number or function defect, and complement deficiency according to the adaptive (B- or T-lymphocyte deficiency) or innate (defects of neutrophil number or function or complement deficiency) immune dysfunctions[6].

Asthma

The diagnosis of asthma was made according to Global Initiative for Asthma guidelines (GINA)[7]. When we briefly look at the patient population, patients who were older than five years had a history of multiple episodes of wheezing with at least a 12% improvement in forced expiratory volume in 1 second (FEV_1) following bronchodilator therapy, whereas patients who were five years old or younger had a history of recurrent respiratory symptoms, a strong family history of asthma in first-degree relatives, and/or atopy presenting as atopic dermatitis, food allergy and/or allergic rhinitis.

Allergic Rhinitis

A diagnosis of allergic rhinitis was accepted as positive in patients whose parents answered in the affirmative to the question "Since birth, has your child had nasal discharge, nasal congestion, nasal itching or sneezing without the presence of the common cold or a flu-like infection?".

Atopic Dermatitis

Atopic dermatitis was defined as a positive response to the question "Have you ever had an itchy rash which continued intermittently for at least 6 months?".

Food Allergy

Skin prick tests and serum-specific IgE measurements were performed for the suspected food in patients with a history of food allergy. Serum-specific IgE was measured using the Immuno-CAP system (Phadia; Uppsala, Sweden). Food allergy diagnosis was confirmed with oral food challenge test.

Allergy Skin Prick Tests

Allergy skin prick testing was performed in all patients for *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* cat and dog dander, Alternaria, cockroach, Aspergillus, Cladosporium, Betulaceae, grass mix, tree mix, Artemisia, Oleaceae, Salicaceae, Parieteria, egg, wheat, peanut, hazelnut, milk, sesame, soya, fish, histamine, and negative controls (Stallergens; Antony, France). These tests were performed on the volar surface of both forearms, with results recorded after 15 minutes. Results were considered positive when the mean wheal diameter was at least 3 mm larger than that produced by the control.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) program. Values were either provided as numbers and percentages or as mean±standard deviation, where applicable. Comparisons of the frequency of allergic diseases and other variables between patients with PID were made using the chi-square test, Fisher's exact test and Student's t-test. A p value of ≤ 0.05 was considered indicative of statistical significance.

Results

The mean age of the patients was 7.4±5.0 years, and 65.3% were male. Within the study group, 82.4% of the patients had antibody deficiency, 10.4% combined immunodeficiency, 6.6% phagocyte number or function defect, and 0.6% complement deficiency. Data including age, frequency of asthma, history of allergic disease symptoms, and skin prick test positivity of all patients are shown in Table I.

Allergic evaluation revealed that 65.1% of the patients had ever wheezing, 45.3% current wheezing, 37.4% a history of allergic rhinitis, and 24.5% a history of atopic dermatitis. In addition, 2.8% of patients had food allergy, 18.6% had a positive skin prick test, and 17% were diagnosed with asthma.

The two most frequently observed groups of antibody deficiencies were selective IgA deficiency and IgG subclass deficiency. When these two groups were compared, those with selective IgA deficiency had a more significant history of ever wheezing (p=0.022). Moreover, the frequency of asthma was higher in those with selective IgA deficiency than in those with IgG subclass, but there was no statistically significant difference (p=0.103). Other histories of individual and familial atopy were similar between the two groups (Table II).

When partial IgA deficiency and IgG subclass

deficiency groups were compared, there was no statistically significant difference in the frequency of asthma, history of individual and familial atopy, and laboratory findings. Furthermore, when the two patient groups with IgA deficiency (selective IgA deficiency and partial IgA deficiency) were compared, there was no statistically significant difference in the frequency of asthma, history of individual and familial atopy, and laboratory findings.

Total IgE levels in patients with selective IgA deficiency and IgG subclass deficiency were significantly higher than in patients with common variable immunodeficiency (CVID) ($p<0.001$ and $p=0.002$, respectively). However, the frequency of asthma and histories of individual and familial atopy were similar.

Among the patients who had food allergy (n=9), 3 had hyper IgE syndrome, 3 had transient hypogammaglobulinemia, 2 had Wiskott-Aldrich syndrome, and 1 had CVID. All of them had positive skin prick tests and all except one had a positive specific IgE against the particular food responsible for the allergy. The patient with negative specific IgE for suspected food had CVID. Four patients had a history of egg allergy, 3 had a history of milk allergy and 2 had a history of nut allergy.

The frequency of asthma and history of current wheezing were higher in patients with antibody deficiency than in patients with combined immunodeficiency. However, the difference in frequency of asthma was not statistically significant ($p=0.127$ and $p=0.049$, respectively). Additionally, parental history of asthma and/or allergic rhinitis was higher in patients with antibody deficiency than in patients with combined immunodeficiency ($p=0.005$). Contrary to this, the frequency of food allergy and total IgE levels were significantly higher in patients with combined immunodeficiency than in patients with antibody deficiency ($p=0.001$ and $p=0.006$, respectively) (Table III).

Mean food-specific IgE level was higher in those with combined immunodeficiency than in those with antibody deficiency. However, there was no statistical significance, which may be related to the few number of patients ($p=0.353$). The mean age of combined immunodeficiency patients with food allergy was 7.0 ± 4.4 years, while that of antibody deficiency patients with food allergy was 2.1 ± 1.3 years ($p=0.067$).

The frequency of asthma and history of current wheezing were higher in patients with antibody deficiency than in patients with phagocyte number or function defect; however, the difference was not statistically significant ($p=0.085$ and $p=0.075$, respectively). Allergic rhinitis, atopic dermatitis and parental history of atopy were more significant in patients with antibody deficiency than in patients with phagocyte number or function defect ($p=0.035$, $p=0.003$ and $p<0.001$, respectively). On the contrary, total eosinophil counts and total serum IgE levels were significantly higher in patients with phagocyte number or function defect than in patients with antibody deficiency ($p=0.003$ and $p=0.001$, respectively) (Table III).

History of atopic dermatitis and frequency of food allergy were more significant in patients with combined immunodeficiency compared to patients with phagocyte number or function defect. However, the frequency of food allergy did not reach a statistical significance because of the low number of patients ($p=0.052$). The other histories of individual or familial atopy, total IgE levels, total eosinophil counts, and skin prick test positivity were similar in the two groups (Table III).

The recurrence of infections apparently decreased with the administration of intravenous immunoglobulin (IVIG), interferon gamma or granulocyte colony-stimulating factor (G-CSF) in patients with combined immunodeficiency and with phagocyte number or function defect. The mean age for commencement of these treatments was 1.9 ± 2.6 years in patients with positive skin prick test and 3.5 ± 3.7 years in those with negative skin prick tests; however, this difference was not statistically significant ($p=0.085$).

Discussion

The frequency of allergic disease in patients with PID was evaluated in this study. Almost two-thirds of the patients had ever wheezing, half of the patients had a history of current wheezing, one-third had allergic rhinitis, one-fourth had atopic dermatitis, and one-fifth had asthma. As much as recurrent respiratory tract infections are confused with allergic rhinitis and asthma symptoms, the frequency of asthma and history of allergic disease in our patients were apparently higher than in the general population according to a phase 2 International Study of

Table I. Asthma, History of Allergic Diseases and Skin Prick Test Positivity in Patients with Primary Immunodeficiency

Diagnosis	Total Patients N=318	Age, year mean±SD	Asthma n (%)	Ever wheezing n (%)	Current wheezing n (%)	Allergic rhinitis n (%)	Atopic dermatitis n (%)	Skin prick test positivity n (%)
Antibody deficiency	262 (82.4)	7.1±4.9	49 (18.7)	180 (66.7)	129 (47.8)	106 (39.3)	66 (24.4)	49 (18.1)
Transient hypogammaglobulinemia	104 (32.7)	2.8±1.8	20 (19.2)	75 (72.1)	63 (60.6)	32 (30.8)	30 (28.8)	16 (15.4)
Selective IgA deficiency	66 (20.7)	9.2±3.9	16 (24.2)	48 (72.7)	28 (42.4)	31 (47.0)	15 (22.7)	13 (19.7)
IgG subclass deficiency	43 (13.5)	9.3±4.1	5 (11.6)	22 (51.2)	16 (37.2)	22 (51.2)	8 (18.6)	8 (18.6)
Common variable immunodeficiency	25 (7.9)	11.3±4.9	3 (12.0)	15 (60.0)	11 (44.0)	10 (40.0)	7 (28.0)	4 (16.0)
Partial IgA deficiency	20 (6.3)	8.7±4.9	4 (20.0)	13 (65.0)	9 (45.0)	10 (50.0)	6 (30.0)	3 (15.0)
X-linked agammaglobulinemia	4 (1.3)	16.0±4.0	1 (25.0)	3 (75.0)	0 (0.0)	0 (0)	0 (0)	1 (25.0)
Combined immunodeficiency	33 (10.4)	10.0±5.0	3 (9.0)	13 (46.4)	10 (30.3)	5 (15.2)	11 (36.4)	7 (21.2)
Severe combined immunodeficiency	7 (2.2)	1.1±3.5	0 (0)	5 (71.4)	4 (57.1)	0 (0)	1 (14.3)	2 (28.6)
Hyper IgE syndrome	7 (2.2)	11.1±5.0	1 (14.3)	5 (71.4)	1 (14.3)	3 (42.9)	7 (100)	4 (57.1)
Ataxia telangiectasia	6 (1.9)	10.9±3.6	0 (0.0)	1 (16.7)	1 (16.7)	1 (16.7)	0 (0)	0 (0)
Wiskott-Aldrich syndrome	4 (1.3)	10.4±7.2	0 (0.0)	2 (50.0)	1 (25.0)	1 (25.0)	4 (100)	3 (75.0)
Autoimmune lymphoproliferative disease	4 (1.3)	8.9±6.2	1 (25.0)	2 (50.0)	1 (25.0)	1 (25.0)	0 (0)	0 (0)
DiGeorge syndrome	2 (0.6)	10.2±1.8	1 (50.0)	2 (100)	2 (100)	0 (0)	0 (0)	0 (0)
Griscelli syndrome	2 (0.6)	6.5±6.4	0 (0)	0 (0)	0 (0.0)	0 (0)	0 (0)	0 (0)
Chronic mucocutaneous candidiasis	1 (0.3)	11.5	0 (0)	0 (0)	0 (0.0)	0 (0)	0 (0)	0 (0)
Phagocyte number or function defect	21 (6.6)	8.5±4.7	1 (4.8)	13 (61.9)	6 (28.6)	4 (19.0)	0 (0)	5 (23.8)
Chronic granulomatous disease	8 (2.5)	10.8±4.9	1 (12.5)	3 (37.5)	0 (0.0)	1 (12.5)	0 (0)	3 (37.5)
Congenital neutropenia	8 (2.5)	9.1±3.4	0 (0.0)	5 (62.5)	1 (12.5)	1 (12.5)	0 (0)	0 (0)
IL-12 receptor beta deficiency	4 (1.3)	3.8±3.5	0 (0.0)	4 (100)	4 (100)	2 (50.0)	0 (0)	2 (50)
Cyclic neutropenia	1 (0.3)	4	0 (0.0)	1 (100)	0 (0.0)	0 (0)	0 (0)	0 (0)
Complement deficiency	2 (0.6)	8.2±9.6	1 (50.0)	1 (50.0)	1 (50.0)	0 (0)	0 (0)	0 (0)

Table II. Comparison of Selective IgA Deficiency with IgG Subclass Deficiency

	Selective IgA deficiency n=66 (%)	IgG subclass deficiency n=43 (%)	P
Sex (Male)	40 (60.6)	29 (67.4)	0.469
Age, years, mean±SD	9.2±3.9	9.3±4.1	0.840
Asthma	16 (24.2)	5 (11.6)	0.103
Ever wheezing	48 (72.7)	22 (51.2)	0.022
Current wheezing	28 (42.4)	16 (37.2)	0.588
Allergic rhinitis	31 (47.0)	22 (51.2)	0.963
Atopic dermatitis	15 (22.7)	8 (18.6)	0.606
Parental asthma and/or allergic rhinitis	34 (51.5)	20 (46.5)	0.610
Skin prick test positivity	13 (19.7)	8 (18.6)	0.888
Total IgE [med (IQR)]	29 (16-60)	16 (16-16)	0.502
Eosinophil, % [med (IQR)]	1.8 (0.9-3.4)	1.9 (0.9-2.9)	0.995

IQR: Interquartile range.

Asthma and Allergies in Childhood (ISAAC) study done in our country[8]. Moreover, several studies have reported that frequency of allergic disease is high in patients with PID[9-15].

It has been reported that the frequency of atopy and allergic disease increases in patients with selective IgA deficiency[10,11,16-18]. In a recent study carried out in our country, it was reported that 10.7% of school children have physician-diagnosed asthma, 16.9% physician-diagnosed allergic rhinitis, and 2.6% physician-diagnosed eczema[19]. In our study, among the patients with selective IgA deficiency, 24.2% of them were diagnosed with asthma, 47% had a history of allergic rhinitis, and 22.7% had a history of atopic dermatitis. This shows that, as in the previous studies, the frequency of allergic disease is increased in patients with selective IgA deficiency compared to the general population.

Those with severe asthma are being reported to have high IgG subclass deficiency[12,20,21]. However, this group of patients is on high-dose steroids, so it has been thought that the IgG subclass deficiency would reflect an effect of steroid treatment. Correspondingly, it has been reported that IgG subclass levels in non-selected asthmatic patients are not different from levels in the general population[22]. While the history of current wheezing was more significant in patients with selective IgA deficiency than in patients with IgG subclass deficiency in our study, the increased frequency of asthma was not statistically significant.

Most patients with CVID have clinical histories that are suggestive of allergic respiratory diseases. However, the role of atopy in these persons is not well determined because total serum IgE and specific IgE are usually low in these patients[23]. Furthermore, it has been reported that approximately 10% of patients with CVID have had asthma and allergic rhinitis without antigen-specific IgE[24]. In our study, even though the other atopy symptoms were similar, total serum IgE levels were lower in patients with CVID than in patients with selective IgA deficiency and IgG subclass deficiency. Additionally, among the patients with food allergy, one of them with CVID had negative specific IgE for the particular food. This supports the thought that the differentiation to plasma cells from B cells is defective in patients with CVID[25].

Allergic diseases are reported to be seen mostly in hyper IgE syndrome (especially DOCK8 deficiency) and Wiskott-Aldrich syndrome from amongst patients with combined immunodeficiency[26, 27]. There were 11 patients in our study with either hyper IgE or Wiskott-Aldrich syndrome, and all of them had a history of atopic dermatitis. Seven of them had a positive skin prick test and five of them had food allergy. Three of those with food allergy had hyper IgE syndrome, with all of them having DOCK8 deficiency. It is known that there is a T-cell defect in combined immunodeficiency. According to results from previous studies and also from our study, it was thought that Th1 would be defective and Th2 overactivated in some combined immunodeficiencies (hyper

Table III. Comparison of Antibody Deficiency, Combined Immunodeficiency and Phagocyte Number or Function Defect

	Antibody deficiency n=262 (%)	Combined immunodeficiency n=33 (%)	Phagocyte number or function defect n=21 (%)	P1	P2	P3
Sex (Male)	172 (65.6)	20 (60.6)	12 (57.1)	0.567	0.375	0.801
Age±SD	7.1±4.9	8.8±5.6	8.5±4.7	0.065	0.208	0.837
Asthma	49 (18.7)	3 (9.1)	1 (4.8)	0.127	0.085	0.492
Ever wheezing	176 (67.2)	17 (51.5)	13 (61.9)	0.075	0.622	0.454
Current wheezing	127 (48.5)	10 (30.3)	6 (28.6)	0.049	0.073	0.892
Allergic rhinitis	108 (41.2)	7 (21.2)	4 (19.0)	0.026	0.035	0.567
Atopic dermatitis	66 (25.2)	12 (36.4)	0 (0.0)	0.170	0.003	0.001
Food allergy	4 (1.7)	5 (17.9)	0 (0.0)	0.001	0.711	0.052
Parental asthma and/or allergic rhinitis	131 (50.0)	8 (24.2)	2 (9.5)	0.005	0.000	0.160
Skin prick test positivity	45 (17.2)	9 (27.3)	5 (23.8)	0.157	0.443	0.777
Total IgE [med(IQR)]	16 (8-43)	130 (7-1050)	160 (26-660)	0.006	0.001	0.944
Eosinophil, % [med (IQR)]	1.9 (1.0-3.3)	2.8 (0.8-4.4)	3.1 (1.6-6.4)	0.417	0.003	0.180

P1: P value between antibody deficiency and combined immune deficiency. P2: P value between antibody deficiency and phagocyte number or function defect. P3: P value between combined immune deficiency and phagocyte number or function defect.
IQR: Interquartile range.

IgE and Wiskott-Aldrich syndrome) and that both Th1 and Th2 would be defective in some other combined immunodeficiencies (ataxia-telangiectasia).

Staple and colleagues[2] reported that ever wheezing and eczema were more significant in patients with DiGeorge syndrome compared to normal healthy children, whereas there was no significant difference between chronic granulomatous disease patients and normal healthy children. They concluded that atopy was present more in T-cell defect than in phagocyte function defect. In our study, it was shown that apart from food allergy generally being primarily in combined immunodeficiency, individual and familial atopy is mostly in antibody deficiency, followed by combined immunodeficiency, and lastly, phagocyte number or function defect.

In conclusion, it was seen that the frequency of asthma and allergic diseases is high in patients with PID, especially those with antibody deficiency. Thus, patients with antibody deficiency, especially those with selective IgA deficiency, should be evaluated regarding asthma and allergic diseases if recurring respiratory symptoms are present. Some with combined immunodeficiency (hyper IgE and Wiskott-Aldrich syndrome) should be evaluated especially regarding food allergy.

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