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İmmunoloji ve Alerji Kliniğinde Değerlendirilen ve Primer Antikor Eksikliği Saptanan Hastalarda Klinik ve Demografik Özellliklerin Belirlenmesi

Determination of Clinical and Demographic Characteristics in Patients with Primary Antibody Deficiency Evaluated in Immunology and Allergy Clinic

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ÖZ

Giriş: Doğuştan bağışıklık hataları; immün sistemin işleyişinde bozukluklar nedeni ile ortaya çıkan, atopik, enfeksiyöz veya otoimmun hastalıkların oluşumuna yatkınlığın artmış olduğu hastalıklardır. Atopik hastalıklar ve doğuştan bağışıklık hataları bir arada olabilir, birbirini taklit edebilir veya kötüleştirebilir. Biz de immunoloji ve alerji kliniğimize başvurup, selektif IgG, IgA ve IgM eksikliği gibi primer antikor eksikliği tespit edilen hastalarda; atopik hastalık görülme oranı ve çeşidini belirlemeyi amaçladık.

Yöntem: Bu retrospektif çalışmada polikliniğimizde; Eylül 2021 -Eylül 2022 tarihleri arasında muayene edilen 5460 hastanın dosyası incelendi. Primer antikor eksikliği tespit edilen 124 hasta çalışmaya alındı. Hastaların demografik verileri, anne-baba akrabalık durumunun varlığı, atopik hastalık tanıları (Alerjik astım, alerjik rinit, ürtiker-anjioödem, anafilaksi, besin alerjisi, ilaç alerjisi) değerlendirildi. Laboratuvar bulgularından tam kan sayımı, serum immunoglobulin (lg G, IgA, IgM, IgE) düzeyleri kaydedildi.

Bulgular: Yaş ortalaması 44,24± 17,17 olan hastaların 76'sı (%61,29) kadın idi. 28 (%22,50'si) hastanın anne babası arasında akraba evliliği vardı. Hastaların immun yetmezlik tanıları değerlendirildiğinde; 57'sinde (%45,96) IgM eksikliği, 50'sinde (%40,32) IgA eksikliği, 17'sinde (%13,70) IgG alt grup eksikliği olduğu görüldü. Hastaların tanıları; (n=38,%30.64) alerjik rinit, (n=24,%19.35) astım, (n=26, %20.96) ürtiker-anjioödem, (n=13,%10.48) atopik dermatit, (n=1, %0.80) anafilaksi, (n=19,%15.32) ilaç alerjisi ve (n=3,%0.24) gıda alerjisiydi.

Sonuç: Ülkemizde akraba evliliği oranının yüksek olmasından dolayı, primer immün yetmezlik hastalıkları sık görülmektedir. İmmün yetmezliklere bağlı komplikasyonların azaltılabilmesi için; hekimlerin erken tanı ve tedavi konusunda dikkatli olması gerekmektedir. İmmün yetmezlikler alerjik hastalıklar ile birarada olabilmektedir. Hastaları değerlendirirken bu hastalıklar da göz önünde bulundurulmalıdır.

Anahtar Kelimeler: antikor eksikliği, astım, erişkin alerjik hastalıklar, immün yetmezlikler

ABSTRACT

Objective: Innate immune defects are disorders in the functioning of the immune system, resulting in an increased susceptibility to atopic, infectious or autoimmune diseases. Atopic diseases and innate immune defects can coexist, precipitate or worsen each other. We aimed to determine the rate and type of atopic disease in patients who presented to our immunology and allergy clinic and were found to have primary antibody deficiency such as selective IgG, IgA and IgM deficiency.

Method: In this retrospective study, the files of 5460 patients examined in our outpatient clinic between September 2021 and September 2022 were analysed. 124 patients with primary antibody deficiency were included in the study. Demographic data, presence of parental consanguinity, diagnosis of atopic diseases (allergic asthma, allergic rhinitis, urticaria-angioedema, anaphylaxis, food allergy, drug allergy) were evaluated. Among laboratory findings, complete blood count, serum immunoglobulin (IgG, IgA, IgM, IgE) levels were recorded.

Results: The mean age of the patients was 44.24± 17.17 years and 76 (61.29%) were female. 28 (22.50%) patients had consanguineous marriage between their parents. The diagnoses of patients were; (n=38, 30.64%) allergic rhinitis, (n=24, 19.35%) asthma, (n=26, 20.96%) urticaria-angioedema, (n=13, 10.48%) atopic dermatitis, (n=1, 0.80%) anaphylaxis, (n=19, 15.32%) drug allergy and (n=3, 0.24%) food allergy.

Conclusion: Due to the high rate of consanguineous marriages in our country, primary immunodeficiency diseases are common. In order to reduce complications related to immunodeficiencies, physicians should be careful in terms of early diagnosis and treatment. Immunodeficiencies may coexist with allergic diseases. These diseases should also be taken into consideration when evaluating patients.

Keywords: antibody deficiency, asthma, adult Allergic diseases, ımmunodeficiencies

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INTRODUCTION

Primary immunodeficiencies (PIDs) have contributed significantly to our understanding of human immunity to infection. More recently, monogenic variants associated with early and severe autoinflammation, autoimmunity and atopic disease have been identified. In addition to immune deficiencies, innate immune defects (IID) now include monogenic immune dysregulation disorders. These include autoinflammatory conditions affecting the innate immune system and autoimmune and atopic diseases primarily affecting the acquired immune system (1-2).

Atopic diseases such as allergic rhinitis, asthma, urticaria, atopic dermatitis are common and result from dysregulated type 2 immunity driven by T helper type 2 (Th2) cells. Th2 cells are protective for the host when coordinated in response to specific helminth pathogens or toxins, but can also cause tissue pathology when overactive or misdirected to innocuous stimuli. Th2 effector functions are mediated primarily by the secretion of proinflammatory cytokines, including interleukin (IL)-4, IL-5 and IL-13, to activate and recruit effector cells such as mast cells and eosinophils (3-8). T follicular helper (Tfh) cells, which are formed in the context of type 2 immune responses, are primarily found in secondary lymphoid tissues and produce immunoglobulin E (IgE) of the B cell class (9).

In monogenic IID associated with atopy or primary atopic disorders, T cell receptor (TCR) signaling, the balance of regulatory T cells (Tregs), effector T cells and innate immune cell effector mechanisms affecting type 2 inflammation and atopic disease are impaired (10-11). The number of studies investigating the burden of allergic disease in PID, which have a broad spectrum, is limited. Recently, the United States Immunodeficiency Network (USIDNET) study found that the prevalence of both food allergy and atopic dermatitis was lower in patients with PID than in the general population. However, the prevalence of food allergy was found to be particularly high in certain PID groups with CD40 ligand deficiency, primary antibody deficiency, hyper IgE syndrome, combined immunodeficiency (CID) and selective IgA deficiency (SIgAD) (12). Primary antibody deficiency (PAD) is the most common primary immunodeficiency group (13,14). In a study conducted in Iran, asthma was found in 20%, allergic rhinitis in 22% and atopic dermatitis in 9% of patients with primary antibody deficiency, whereas in another report, atopic dermatitis was present in 52% of patients with SIgAD. It is evident that there is a relationship between primary antibody deficiency and atopic disease and that it varies according to the type of antibody found to be deficient (15,16).

We aimed to determine the frequency and type of atopic disease in patients admitted to our immunology and allergy clinic and found to have primary antibody deficiency such as selective IgG, IgA and IgM deficiency.

MATERIALS AND METHODS

In this study, the files of 5700 patients who were examined in our immunology and allergy outpatient clinic between September 2021 and September 2022. 240 patients with missing data were excluded, and the file records of 124 patients with primary antibody deficiency (PAD) among 5460 patients were retrospectively evaluated.

In addition to the demographic data of the patients, the presence of parental consanguinity atopic disease diagnosis allergic asthma, allergic rhinitis, urticaria-angioedema, anaphylaxis, food allergy, drug allergy were evaluated. Clinical history was taken and physical examination was performed. The diagnosis of asthma according to GINA guideline criteria, anaphylaxis according to anaphylaxis guideline, urticaria and angioedema according to urticaria guideline criteria, allergic rhinitis according to allergic rhinitis guideline criteria and atopic eczema according to Hanifin Rajka criteria were confirmed (17-22). Among laboratory findings, hemogram, serum immunoglobulin (IgG, IgA, IgM, IgE) levels were recorded.

Evalution of immune dysregulation

Immune system evaluation included complete blood count and serum immunoglobulin (lgG, lgA, lgM, lgE) levels. Serum immunoglobulin levels were determined by nephelometric method and values were compared with normal limits according to age. Patients with a lymphocyte count <1500/ µL were considered lymphopenic and patients with a neutrophil count <1500/ µL were considered neutropenic (13,24,25). Patients with Ig G levels below 700 mg/dL were diagnosed as selective IgG deficiency, patients with IgA levels below 70 mg/dL were diagnosed as selective IgA deficiency, and patients with IgM levels below 40 mg/dL according to age were diagnosed as selective IgM deficiency (26).

Atopy was determined by IgE positivity specific for any allergen and/or sensitization on skin prick test (SPT) (27).

Comorbid Atopic Diseases

According to the Global Initiative for Asthma (GINA) guidelines, asthma is characterized by variable respiratory symptoms such as coughing, wheezing, shortness of breath, and chest tightness. Additionally, there is variable airflow limitation, which is defined as a FEV1/FVC ratio less than 80%, along with either a >200 mL increase or a >12% variability in FEV1 after using a short-acting bronchodilator or following 4 weeks of anti-inflammatory treatment or between visits (17).

Allergic rhinitis (AR) is defined as an atopic disease characterized by nasal mucus or nasal discharge, sneezing, nasal itching and congestion (18).

Urticaria-angioedema is defined as the occurrence of wheals and/or angioedema for a total duration of six weeks or more (19).

Atopic dermatitis is defined as a chronic, recurrent, pruritic and inflammatory skin disease (20).

Food allergy is defined as a Type I hypersensitivity reaction mediated by specific IgE antibodies developed against food proteins (21).

Drug allergy is one type of adverse reaction to drugs and encompasses a spectrum of hypersensitivity reactions with heterogeneous mechanisms and clinical presentations. (22).

Anaphylaxis is defined as a severe systemic hypersensitivity reaction with sudden onset and may lead to death (23).

The frequency of atopic diseases such as asthma, allergic rhinitis, chronic urticaria angioedema, atopic dermatitis were investigated according

to the antibody deficiency detected among the patients diagnosed with PAD. The study protocol was approved by the local ethics committee of our hospital with decision number 319. The study,

was conducted in accordance with good clinical practice standards and the Declaration of Helsinki.

Statıstıcal Analyses

SPSS software (version 21.0 for Windows; SPSS Inc., Chicago, IL, USA). Parametric variables were presented as means and standard deviations, nonparametric variables are presented as medians and interquartile ranges (IQR). Mann Whitney U test was used to compare continuous variables of two independent groups. $p< 0.05$ was considered statistically significant.

. RESULTS

Primary antibody deficiency was detected in 124 (2.27%) of 5460 patients evaluated in our immunology and allergy clinic. The mean age was 44± 17 years and 76 (61.2%) of the patients were female. 28 (22.5%) patients had consanguineous marriage between their parents.

Sociodemographic characteristics, allergic diseases and immunodeficiency diagnoses of the patients according to antibody deficiencies are shown in Table-1. When the clinical symptoms, examinations of the patients were evaluated; 57 (45.96%) were diagnosed with IgM deficiency, 50 (40.32%) with IgA deficiency and 17 (13.70%) with IgG subgroup deficiency. 44 patients (35.48%) were found to have atopy by skin prick test and/or specific IgE. When the comorbid allergic disease diagnoses of the patients were evaluated; 38 (30.64%) had allergic rhinitis, 24 (19.35%) asthma, 26 (20.96%) urticaria-angioedema, 13 (10.48%) atopic dermatitis, 1 (0.80%) anaphylaxis according to venom, 19 (15.32%) drug allergy and 3 (2.40%) food allergy.

The 3 most common atopic diseases in patients with selective Ig G deficiency were asthma (n=6, 35.29%), drug allergy (n=4, 23.52%), urticaria-angioedema (n=3, 17.64%) and atopic dermatitis (n=3, 17.64%).

The 3 most common atopic diseases in patients with selective Ig A deficiency were allergic rhinitis (n=20, 40%), asthma (n=10,20%) and drug allergy (n=8,16%).

The most common diseases in patients with selective Ig M deficiency were allergic rhinitis (n=18, 31.57%), urticaria angioedema (n=16, 28.07%), and asthma (n=8,14.03%). (Table-2).

Table 1. Demographic Characteristics of Patients with Allergic and Immune Diseases

	All patients with antibody deficiency n:124	Selective Ig G deficiency n:17	Selective Ig A deficiency n:50	Selective Ig M deficiency n:57
Age (year), mean ±SD	44.24±17.17	44.20±16,94	33.65±12.92	53.22±15.19
Gender, Female n (%)	76(63,9)	16(80)	35(71)	25(45)
Neutrophil, Mean± SD	4545.65±1782.81	5329.00±2716.88	4242.97±1717.66	4818.86±1915.36
Lymphocyte, Mean± SD	2199.21±700.25	2209.50±630.79	2160.00±642.17	2212.26±761.58
Eosinophil, Mean± SD	189.13±133.26	208.50±166.01	158.72±126.93	204.15±116.97
Consanguineous marriage n(%)	28(22.5)	4(20)	12(24.5)	12(22)
Presence of atopy n(%)	44(35)	6(30)	19(38)	19(34)

Table 2. Patients' Diagnoses of Allergic, Atopic Diseases and Immunodeficiency

	Selective Ig G deficiency n, (%)	Selective Ig A deficiency n, (%)	Selective Ig M deficiency n, (%)
Allergic rhinitis n:38	0	20(52.7)	18(47.3)
Asthma n:24	6(25.0)	10(41.6)	8(33.3)
Urticaria angioedema n:26	3(11.5)	7(26.9)	16(61.5)
Atopic dermatitis n:13	3(23.0)	4(30.7)	6(46.1)
Anaphylaxis n:1	0	0	1(100)
Drug allergy n:19	4(21.0)	8(42.1)	7(36.8)
Food allergy n:3	1(33.3)	1(33.3)	1(33.3)

DISCUSSION

In our study, the prevalence of PAD was found to be 2.27% (124/5460) in patients presented to our immunology and allergy outpatient clinic with allergic complaints within one year. The reported antibody subgroup deficiencies were IgM (45.96%), IgA (40.32%), and IgG (13.70%), respectively. Mean neutrophil, lymphocyte and eosinophil levels were within normal limits. The rate of consanguineous marriage in the parents was 22.5%. The rate of atopy was 35% and it was observed most frequently in IgA deficiency (35%). The most common atopic disease was allergic rhinitis (30.64%) and the least common atopic disease was anaphylaxis (0.8%).

When the rate of atopic diseases was analyzed according to subgroup deficiencies, atopic diseases involving the respiratory system such as asthma and allergic rhinitis were observed in IgA deficiency (28), while atopic diseases involving the cutaneous-subcutaneous tissue such as chronic urticaria-angioedema and atopic dermatitis were most frequently observed in IgM deficiency (29).

In a study conducted by Kılıç et al. including two centers in Turkey, the prevalence of PID was reported as 30.5/100000 and the most common type of PID was PAD (73.5%). However, the prevalence of PID among pediatric patients admitted to a specific immunology and allergy unit in Ankara was found to be 2.1%, similar to our study (30).

However, although the most common antibody deficiency among PAD has been reported as IgA (1/333-1/700) (31), IgM was observed in our study. This may be due to the differences in the populations included in the study, especially between children and adults. For example, IgM deficiency was found to be 0.1-3.8% in hospitalized patients, 1.68% in unselected community health screening and 0.07% in immunology and allergy clinic (32). Similarly, in our study, selective IgM deficiency (1%) was detected in 57 patients among 5460 patients screened in our immunology and allergy outpatient clinic.

The incidence of autosomal recessive diseases increases in the presence of consanguineous marriage. While the rate of consanguineous marriage was found to be 34% in patients with antibody deficiency by Yorulmaz et al., this rate was found to be 21.6% in patients by Mısırlıoğlu et al. (31,33). In our study, the rate of consanguineous marriage was found to be 22.5%.

In order to provide a worldwide overview of allergic diseases across a which broad spectrum of IIDs, the largest study of pediatric and adult patients from 30 centers in 23 countries was recently published. The rate of atopic disease was 16.6% and 68.8% according to The United States Immunodeficiency Network (USIDNET) data (34). In our study, since patients admitted to our immunology and allergy clinic were included in the study, all of them had at least one atopic disease finding among their complaints. In this study, as in our study, the most common atopic diseases were asthma (46.9%), atopic dermatitis (23.70%) and allergic rhinitis (8.20%). However, in our study, allergic rhinitis was found to be the most common atopic disease rather than asthma. The reason for this is that in this study, atopic diseases were determined through a questionnaire, whereas in our study, the diagnostic criteria of the guidelines were taken as the basis as stated in the methodology. It was noticed that urticaria-angioedema and drug allergy, which were found most frequently in our study, were not questioned in the study mentioned above (34). In a study conducted in our country including pediatric patients in which the history of urticaria was also questioned, the frequency of urticaria in PID patients was reported as 6.2% (31). This may be due to the fact that chronic urticaria and angioedema are encountered more frequently in adults.

Selective IgM deficiency is characterized by low IgM level and serum IgM level is below 40 mg/dl (35). When the literature is reviewed, it has been observed that atopy, asthma and allergic rhinitis are more frequent in patients with IgM deficiency compared to the normal population (36,37). In a study by Goldstein et al. it was observed that the frequency of idiopathic anaphylaxis and angioedema was higher in patients with selective Ig M deficiency compared to the general population (38).

In our study, urticaria angioedema and anaphylaxis were observed with the highest rate in patients with IgM deficiency.

In a study in which 131 patients with IgA deficiency were evaluated, it was reported that allergy (asthma, atopic dermatitis, allergic rhinitis) was observed with the second frequency after recurrent infections (39). In its pathophysiology; deficiency of IgA leads to failure in preventing general environmental antigens from reaching the immune system and causes allergy. It has also been reported that IgA antibodies have a suppressive role in mediator release and its elimination in deficiency leads to mediator release (40). Considering the effect of IgA in secretions on the immune pathway, it is not surprising that atopic diseases involving the airways were observed more frequently in patients with IgA deficiency in our study.

It is observed that atopy and response to environmental allergens frequently occur in Ig G deficiency (41,42). IgG subgroup deficiency was not evaluated in our patients. In these patients, the order of atopic disease seen in other subgroup deficiency is slightly different; asthma, atopic dermatitis and urticaria have been reported, respectively.

CONCLUSION

Patients with selective antibody deficiencies may present to immunology and allergy clinics with allergic symptoms. Especially IgM and IgA deficiency is common in adult patients. The atopic diseases detected in these patients may vary according to the type of antibody deficiency. Urticaria-angioedema and anaphylaxis are more common in IgM deficiency, while atopic diseases involving the airways such as allergic rhinitis and asthma are more common in IgA deficiency. Drug allergy has not been considered in many studies so far; drug allergy should be questioned especially in patients with IgM deficiency. Although this prevalence study has limitations such as its retrospective nature and lack of verification with tertiary immunologic tests, it will be instructive in establishing a link between immunodeficiency and different atopic diseases.

Ethics Committee Approval: The study protocol was approved by the local ethics committee of University of Health Sciences, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital,

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