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Relationship of Selective IgE Deficiency with Autoimmune Diseases

Selektif IgE Eksikliği ve Otoimmun Hastalık İlişkisi

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Abstract

Aim: Selective IgE deficiency (SIgED) is currently defined as a significant decrease in serum levels of immunglobulin E (IgE) (≤2 kU/L) in a patient whose other immunoglobulin levels are normal. The clinical spectrum of SIgED is unknown still. This study aimed to determine the relationship between SIgED and autoimmune diseases in an allergy and immunology clinic of a university hospital.

Material and Method: A retrospective study of the data obtained from medical records of 40 patients, 27 were female (67.5%), and the mean age was 39 years (range 20–69 years) and IgE levels of ≤2.0 kU/L with normal immunglobulin G (IgG), immunglobulin A (IgA), immunglobulin M (IgM) levels.

Results: A total of 40 patients , 27 females (67.5 %) and 13 males (32.5%), were included in the study. The mean age of the patients was 39±13.06 years (range 20–69). In the present study, 35% of patients had an autoimmune disease (N:14), however 65% of patients did not have any autoimmune disease (N:26). Hashimoto's thyroiditis being the most frequent (N:6) in 15% which is followed by systemic lupus erythematosus (SLE) (N:3) in 7.5%, celiac disease (N: 2) in 5%, chronic spontaneous urticaria (CSU), vitiligo and type 1 diabetes mellitus (DM) (N:1) in 2.5%.

Conclusion: SIgED, should be defined clearly with cut-off values of IgE. Physicians should show more attention to the low IgE values and investigate patients about autoimmune diseases which can be seen together with SIgED. More studies should be conducted to investigate associated diseases with SIgED.

Keywords: Immunoglobulin E, autoimmune disease, selective Immunglobulin E deficiency

Öz

Amaç: Selektif IgE eksikliği (SIgED), günümüzde diğer immünglobulin düzeyleri normal olan bir hastada serum immunglobulin E (IgE) düzeylerinde (≤2 kU/L) anlamlı bir azalma olarak tanımlanmaktadır. SIgED'in klinik spektrumu hala bilinmemektedir. Bu çalışmada bir üniversite hastanesinin alerji ve immünoloji kliniğinde SIgED ile otoimmün hastalıklar arasındaki ilişkinin belirlenmesi amaçlandı.

Gereç ve Yöntem: 27'si kadın (%67,5) yaş ortalaması 39 (dağılım 20-69) ve IgE düzeyi ≤2,0 kU/L iken immunglobulin G (IgG), immunglobulin A (IgA), immunglobulin M (IgM) seviyeleri normal olan 40 hastanın tıbbi kayıtlarından elde edilen veriler retrospektif olarak incelendi.

Bulgular: Çalışmaya 27'si kadın (%67,5) ve 13'ü erkek (%32,5) olmak üzere toplam 40 hasta dahil edildi. Hastaların yaş ortalaması 39±13,06 yıl (dağılım 20-69) idi. Çalışmamızda hastaların %35'inde otoimmün hastalık mevcuttu (N:14), ancak hastaların %65'inde herhangi bir otoimmün hastalık yoktu (N:26). Hashimoto tiroiditi %15 ile en sık görülen (N:6) olup, bunu %7,5 ile sistemik lupus eritematozus (SLE) (N:3), %5 ile çölyak hastalığı (N:2), kronik spontan ürtiker (KSU), vitiligo ve tip 1 diyabetes mellitus (DM) (N:1) %2,5 takip etmektedir.

Sonuç: SIgED, IgE için belirlenecek eşik değerleri ile net bir şekilde tanımlanmalıdır. Klinisyenerin düşük IgE değerlerine daha fazla dikkat etmesi ve hastaları SIgED ile birlikte görülebilen otoimmün hastalıklar açısından araştırmaları gerekmektedir. SIgED ile ilişkili hastalıkların araştırılması için daha fazla çalışma yapılmalıdır.

Anahtar Kelimeler: İmmunglobulin E, otoimmun hastalık, selektif İmmunglobulin E eksikliği

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INTRODUCTION

Immunoglobulin E (IgE) was discovered in 1966, and we have begun to understand the role of IgE in the development of autoimmunity.[1] Since then, the immune system and the mechanisms leading to autoimmunity continue to be studied. It's known that IgE had important function in the immune system against infections with helminths and elevated serum levels are associated with, parasitic infections, allergic disorders, and specific immunologic disorders but the implications of ultra-low IgE levels are not understood clearly.[2,3] IgE is located bound to the high-affinity receptor (FcεRI) on the surface of basophils and mast cells mostly. When specific IgE/FcεRI and allergen complex occurs, the degranulation of basophils and mast cells begins and different mediators (bronchoconstrictors, vasoactive mediators, interleukins) are released, which create the clinical findings of the allergic reaction (asthma, rhinitis, urticaria, anaphylaxis, angioedema).[4]

According to the recent classification, innate errors of immunity were separated into 10 groups, one of which is "antibody deficiencies" (Group 3).[5,6] immunglobulin M (IgM), immunglobulin G (IgG), immunglobulin A (IgA) have a central role in the humoral immune response. Also, these immunoglobulins play an important role in fighting against viral, bacterial, protozoal, and parasitic infections. They create the defense mechanism so-called acquired immunity mediated by antibodies.[7] In some types of immunodeficiencies, levels of one or more of IgG, IgM, and IgA immunoglobulins are recognized.[5,6] Selective IgE deficiency (SIgED) is defined as normal IgA, IgM and IgG levels in a patient with significantly low serum IgE levels (≤2 kIU/L).[8]

Common variable immunodeficiency (CVID) is the most common combined form and characterized by reduced serum levels of IgG, with a reduction of IgM or IgA, or both. CVID is associated with increased risk of malignancy, autoimmune disorders, granulomatous diseases, recurrent sinopulmonary infections and altered antibody response against various infections.[9,10] Patients who have normal serum IgM and IgA levels but low serum IgG levels are considered to have selective IgG deficiency (SIgGD). The CVID group was more likely to have a higher incidence of granulomas, autoimmune cytopenias, splenomegaly, bronchiectasis, lymphoid neoplasms, and poorer responses to vaccines according to the studies comparing the CVID and SIgGD.[11] IgG subclass deficiency (IgGSD) is a subset of primary immunodeficiencies, that have the triad of low IgG response against pneumococcal vaccines, decreased levels of one or more of the IgG subclasses, and severe or frequent respiratory tract infections.[12,13] Selective IgM (SIgMD) and selective IgA deficiency (SIgAD) are defined in asymptomatic patients as well as people with allergic diseases, recurrent infections, autoimmune processes, and malignant tumors.[14-16]

Serum IgE values between (≤2 kU/L) and up to 100 kU/L are considered normal. There is not a universally accepted minimum level to define IgE deficiency, but an excess of IgE (>100 kU/L) can be established. Researchers used various cut-off points to establish IgE deficiency.[14-17] Most clinicians consider very low or even unmeasurable (≤2 kU/L) IgE values generally "normal" and not pathological. Low levels of IgE is associated with CVID frequently.[18-20] For the diagnosis of CVID, it may be recommended to use routine IgE measurement first, according to the literature.[19,20] The presence of low IgE values is usually associated with some of the other immunoglobulin deficiencies in the classification of primary immunodeficiencies.[5,6] The presence of SIgED alone was not considered in the immundeficiency classification. It has been shown that patients with normal values of other immunoglobulins but a low level of IgE, have generally autoimmune diseases, similar to those patients with CVID, IgGSD or with SIgGD, SIgAD, and SIgMD.[8-11,21-25] SIgED has a relationship with various diseases similar to that seen in other antibody deficiencies, but its clinical spectrum is unknown still. We aimed to determine the association between SIgED and autoimmune diseases in an allergy and immunology clinic of a university hospital.

MATERIAL AND METHOD

Patients who have an IgE concentration ≤2 kU/L with normal IgG, IgM, and IgA concentrations applied to the allergy immunology clinic for any reason between July 2022-2023 was included in the study. A total of 5300 medical records were investigated, of whom 155 patients have IgE concentration ≤2 kU/L, 40 patients have IgE concentration ≤2 kU/L with normal IgG, IgM, and IgA concentrations were included in the study shown in **Figure 1**. Of the 40 patients, 27 were female (67.5%), and the mean age was 39 years (range 20–69 years). Skin prick tests (SPTs) are performed in our clinic with a panel of common allergenic extracts of the aeroallergens in our region in patients with a suspicion of respiratory or food allergy routinely.

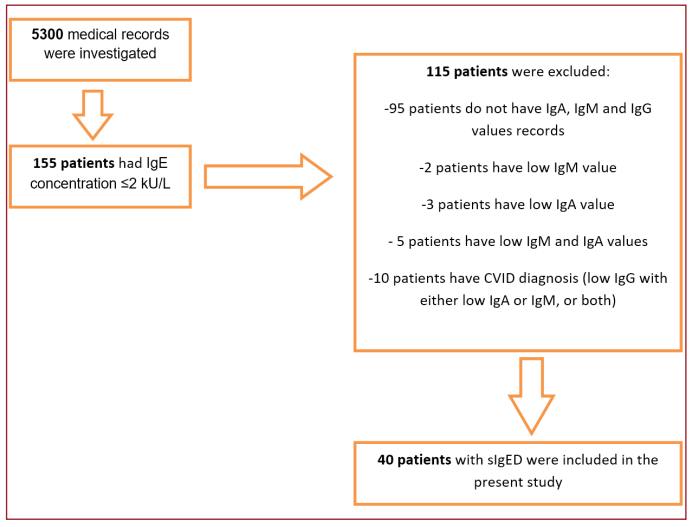

Figure 1. Flow chart of patients analyzed.

Ethical Statement

The study was approved by Manisa Celal Bayar University Clinical Researches Ethics Committee (Date: 15.06.2022, Decision no: 20.478.486/1391). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

The data obtained were evaluated by descriptive statistics (number, mean, percentage distribution, standard deviation, range etc.). Categorical variables were evaluated using Fisher's exact test. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 40 patients were included in the present study. Twenty seven patients were females (67.5%) and 13 patients were males (32.5%). The mean age of the patients partcipating in the study was 39±13.06 years (range 20–69). In the present study, 35% of patients had an autoimmune disease (N:14), however 65% of patients did not have any autoimmune disease (N:26). Investigating the disease spectrum individually, Hashimoto's thyroiditis (N:6) in 15%, systemic lupus erythematosus (SLE) (N:3) in 7.5%, celiac disease (N: 2) in 5%, chronic spontaneous urticaria (CSU) (N:1) in 2.5%, vitiligo (N:1) in 2.5%, type 1 diabetes mellitus (DM) (N:1) in 2.5% were detected (**Table 1**).

Table 1: Autoimmune disease frequency of participants.

Autoimmune Disease	Female (N:27)	Male (N:13)
Hashimato's Thyroiditis	4 (14.8%)	2 (15.4%)
Celiac Disease	1 (3.7%)	1 (7.7%)
SLE	3 (11.1%)	0 (0%)
CSU	0 (0%)	1 (7.7%)
Vitiligo	1 (3.7%)	0 (0%)
Type 1 DM	1 (3.7%)	0 (0%)
Autoimmune disease	17 (63%)	9 (69.2%)

SLE: Systemic lupus erythematosus; CSU: Chronic spontaneous urticaria; DM: Diabetes mellitus.

Seventeen females did not have an autoimmune disease (63%) and 10 females had an autoimmune disease (32.5%). Of the female patients with autoimmune disease, 14.8% had Hashimoto's thyroiditis(N: 4), 11.1% had SLE (N: 3), 3.7% had celiac disease (N: 1), 3.7% had vitiligo (N: 1) and 3.7% had type 1 DM (N: 1). While 9 males did not have an autoimmune disease (69.2%), 4 males had an autoimmune disease (30.8%). Of the male patients with autoimmune disease, 15.4% had Hashimoto's thyroiditis(N: 2), 7.7% had celiac disease (N: 1) and 7.7% had CSU (N: 1).

Of those patients with autoimmune disease, 71.42% were females (N: 10) and 28.58% were males (N: 4). There was no statistically significant difference between gender and having an autoimmune disease (p:0.491). In the present study, 52.5% of the patients had a total IgE of 2.00 (N: 16), 40% had a total IgE of 1 (N: 21), and 7.5% had a total IgE of 0 (N: 3). Mean of serum IgA, IgM, and IgG values of the participants were: IgM 101.87 (range, 18.3–319) mg/dL (normal values (40-230 mg/dL), IgG 1034.20 (range, 552-1830) mg/dL (normal values 700-1600 mg/dL), and IgA 157.45 (range 26.8-352) mg/dL (normal values 70-400 mg/dL). Serum levels of IgG1, IgG2, IgG3, and IgG4 had been assessed in 3, 7, 5 and 5 patients respectively and were normal in all patients, one with low IgG2. SPT results were normal in all patients.

DISCUSSION

An important number of CVID patients had autoimmune diseases (27%).[26] It has been shown that SIgMD,[24,27,28] SIgGD.[12,22] IgGSD (29), and SIgAD.[22,23] are also associated with organ-specific and systemic autoimmune diseases. The clinical manifestations of autoimmune diseases in CVID and other selective immunodeficiencies are various including a plethora of hematologic (thrombocytopenic purpura, cytopenia, Evans syndrome, hemolytic anemia), and non-hematologic diseases (rheumatoid arthritis, autoimmune thyroid diseases, Sjögren´s syndrome, unspecific inflammatory arthritis, SLE, autoimmune hepatitis).[30] In this study Hashimoto's thyroiditis was the most frequent autoimmune disease similar to the literature.[31] Our finding about the relationship between autoimmune diseases and SIgED is similar to the literature that investigated the relationship between deficiencies in other immunoglobulin classes with autoimmune diseases.

The mechanism of protecting against autoimmune reactivity of both IgE and IgA may be by promoting the mucosal exclusion of exogenous antigens. It's known that, SIgAD have a high relationship between autoimmune diseases similar to IgE hypogammaglobulinemia, including rheumatoid arthritis, SLE, Sjogren's syndrome, autoimmune thyroiditis and pernicious anemia. IgA prevents systemic absorption of mucosal antigens and as a result, may protect against autoimmunization. Deficient defense at the mucosal barrier could allow autoimmune responses occurring by the exogenous antigens to be induced by several mechanisms like stimulating autoreactive lymphocytes through molecular mimicry, promoting immune complex formation, superantigen-induced polyclonal activation of lymphocytes, inducing a perturbation of the idiotypic network, and/or by aberrant induction of MHC class II antigens.[21,22] Also, one possible cause may be the lack of protection against the crossing of the mucosal barrier by infectious agents that can trigger autoimmune disease. Another possible explanation for the association between SIgAD and autoimmune disease may be common genetic factors predisposing to both immunoglobulin deficiency and autoimmune phenomenon.

In another study, the association of SIgED with hematological and non-hematological autoimmune diseases was similar to that described in other immunodeficiencies.[31] In the literature, in adults and children with SIgED, isolated and mixed autoimmune diseases were significantly more

common than control populations. Autoimmune diseases reported in patients with SIgED were thyroid diseases, SLE, arthritis, and cytopenias in the literature.[8,21] In conclusion, these findings sustain that autoimmune diseases have relationship with the SIgED.

Additional studies showing an increased association between SIgED with autoimmune diseases compared with healthy controls are needed to demonstrate the relationship between SIgED and autoimmunity.

The limitations of this study was single-centered, the small sample size of patients recruited and its retrospective nature. Also, we used a very low cut-off limit (IgE≤2.0 kU/L) to have specific diagnostic criteria for SIgED. However, patients who have an IgE value close to this level could also have similar associated autoimmune diseases. New studies with different cut-off points for serum IgE level should be conducted.

CONCLUSION

SIgED, should be defined clearly with cut-off values of IgE. Physicians should show more attention to the low IgE values and investigate patients about autoimmune diseases which can be seen together with SIgED.. We wanted to take attention to a spectrum of diseases that may be underestimated in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Manisa Celal Bayar University Clinical Researches Ethics Committee (Date: 15.06.2022, Decision no: 20.478.486/1391).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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