ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Investigation of the Relationship Between Disease Activity Scores, Serum Parameters and Skin Prick Test in Patients with Atopic Dermatitis and Chronic Spontaneous Urticaria: A Cross-Sectional Study

Atopik Dermatit ve Kronik Spontan Ürtikerde Hastalık Aktivite Skoru, Serum Parametreleri ve Deri Prick Testi Arasındaki İlişkinin Araştırılması: Kesitsel Çalışma

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ABSTRACT Objective: Atopic dermatitis and chronic spontaneous urticaria are allergic skin diseases with recurrent attacks. In this study, disease activity score and laboratory parameters were investigated in patients with atopic dermatitis and chronic spontaneous urticaria. **Material and Methods:** A total of 68 patients including 33 atopic dermatitis and 35 chronic spontaneous urticaria patients from the dermatology outpatient clinics were enrolled in this study. Serum levels of total immunoglobulin E (IgE), blood eosinophil and basophil counts; prevalence of sensitization to aeroallergens, and disease activity scores were compared between the two groups. **Results:** A higher eosinophil count in the peripheral blood was observed in atopic dermatitis patients compared to chronic spontaneous urticaria patients. Disease activity scores (SCORAD index) were positively correlated with the eosinophil count and total IgE levels. Furthermore, it was found that the basophil count increased while total IgE levels and SCORAD index scores decreased in the chronic period of the disease. Total IgE levels and SCORAD index scores were higher in atopic dermatitis patients with a positive skin prick test. In chronic spontaneous urticaria patients, it was observed that basophil counts and total IgE levels were correlated, but there was not a correlation between disease activity scores, skin prick test results, and levels of other laboratory parameters. **Conclusion:** The relationship of serum parameters, especially IgE levels, with the disease activity was found to be significant only in atopic dermatitis.

Keywords: Atopic dermatitis; urticaria; basophil; IgE

ÖZET Amaç: Atopik dermatit ve kronik spontan ürtiker, tekrarlayan atakları olan alerjik deri hastalıklarıdır. Bu çalışmada, atopik dermatitli ve kronik spontan ürtikerli hastalarda hastalık aktivite skoru ve laboratuvar parametreleri araştırıldı. **Gereç ve Yöntemler:** Bu çalışmaya, 33 atopik dermatit ve 35 kronik spontan ürtiker hastası olmak üzere toplam 68 hasta dâhil edildi. İki grup arasında total immunglobulin E (IgE), serum eozinofil ve bazofil değerleri, aeroalerjenlere karşı duyarlılık ve hastalık aktivite skorları karşılaştırıldı. **Bulgular:** Kronik spontan ürtiker hastalarına kıyasla atopik dermatitli hastalarda periferik kanda daha yüksek eozinofil sayısı gözlendi. Hastalık SCORAD indeks, eozinofil sayısı ve total IgE seviyeleri ile pozitif korelasyon gösterdi. Ayrıca hastalığın kronik döneminde bazofil sayısının arttığı, total IgE düzeyleri ve SCORAD indeks skorlarının azaldığı belirlendi. Deri prick testi pozitif olan atopik dermatitli hastalarda, total IgE seviyeleri ve SCORAD indeks skorları daha yüksekti. Kronik spontan ürtiker hastalarında bazofil sayıları ile toplam IgE düzeyleri arasında korelasyon olduğu; ancak hastalık aktivite skoru, deri prick test sonuçları ve diğer laboratuvar parametre düzeyleri arasında korelasyon olmadığı tespit edildi. **Sonuç:** Serum IgE düzeylerinin hastalık aktivitesi ile ilişkisi sadece atopik dermatitte anlamlı bulundu.

Anahtar Kelimeler: Atopik dermatit; ürtiker; bazofil; IgE

Atopic dermatitis (AD) is a chronic, itchy skin disease with genetic and immunological factors in the etiology. AD affects 20-25% of children and 2-3% of adults.[1] Both Type-1 and Type-4 delayed-type hypersensitivity reactions are known to be involved in the pathogenesis of the disease. In AD, 80% of pa-

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tients have defective cellular immunity. Along with the suppression of T-lymphocytes, B-lymphocytes leads to increases in immunoglobulin E (IgE) synthesis. A Th2 cytokine response is more prominent in early disease and a Th1 cytokine response is more prominent in chronic lesions. In early disease stages; interleukin (IL)-4, IL5, IL-6 release from Th 2 cells increase, B-cell proliferation and IgE secretion increase, and eosinophils become activated. While CD4-positive T cells are more abundant in inflammatory skin infiltrates in acute AD, there is mainly dermal mononuclear cell infiltration with the predominance of macrophages in chronic disease stages.[2]

Chronic spontaneous urticaria (CSU) affects 0.1-0.8% of the population.[3] The pathophysiology of CSU is examined under 3 categories as allergic, autoimmune, and drug-induced or inducible urticaria. In allergic urticaria, the allergen stimulates the synthesis of IgE that binds to FcεRI leading to the degranulation of mast cells and basophils. Synthesis of IgG autoantibodies against the FcεRI alpha-subunit or against IgE antibodies has been observed in autoimmune urticaria. Such autoantibody cross-linking of FcεRI leads to histamine release via the degranulation of mast cells and basophils.[4]

Skin prick testing (SPT) is used to investigate Type-1 hypersensitivity. The test shows that specific IgE antibodies are present in the tissue.[5] Sensitivity develops in the first encounter with an antigen taken by inhalation or through skin contact or the oral route. The 2nd encounter with the same antigen leads to an allergic response.

In this study on AD and CSU patients; we planned to investigate serum total IgE levels, eosinophil and basophil counts, SPT results, and disease activity scores, and to analyze the correlation of these parameters with each other.

MATERIAL AND METHODS

This study was carried out through the retrospective examination of data from 36 AD and 36 CSU patients making a total of 72 patients, who attended the dermatology outpatient clinics of hospital in the period between December 2018-April 2019. The study was approved by the S.B.Ü Kocaeli Derince Training and Research Hospital Clinical Research Ethics Committee (date: Jun 27, 2019, no: 2019-46) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. The study has been done by protecting animal rights.

The diagnosis of CSU was made by clinical examinations and the diagnosis of AD was made by clinical examinations and using the Hanifin Rajka criteria. Individuals; who were 18-65 years old, who had a history of urticaria lasting for more than 6 weeks and having at least 2 attacks per week, and individuals, who had a biopsy-confirmed diagnosis of AD with supporting clinical findings were included in the study. Patients with a history of medication use and systemic diseases that can be associated with urticaria were excluded from the study. History of dermatoses including dermographism, physical urticaria, hereditary angioedema, food and/or drug allergy, contact urticaria, collagen vascular diseases and atopic dermatitis, systemic autoimmune disorders were our exclusion criteria in CSU patients. Individuals; who were diagnosed with CSU or AD, who had not used any sedating-nonsedating antihistamines, systemic steroids, antidepressants, and leukotriene receptor blockers for the last 1 month, and who underwent SPT in the last month were selected by reviewing patient files. Eligible patients were included in the study. Age, gender, duration of complaints, disease activity scores, and laboratory and SPT results of patients with CSU and AD were recorded. One patient with CSU and three patients with AD were excluded from the study when we found that they used antihistamines during the study.

All patients in both groups of the study underwent a 20-item SPT including tests for aeroallergens. Complete blood counts and total IgE levels were tested in all study patients, too. Standard allergen extracts (Alk-Denmark), histamine (1 mg/mL) as a positive control and saline as a negative control were used for SPT. In examinations performed 20 minutes after the test, a mean induration diameter of ≥3 mm on the skin was evaluated as positive.

Using a routine hematology analyzer and the total IgE enzyme immunoassay method (Abbott,

USA), eosinophil and basophil counts were measured in blood samples collected from patients.

Urticaria activity scale (UAS7) scores (scores of ≤6 indicating well-controlled, 7-15 indicating mild, 16-27 indicating moderate, and 28-42 indicating severe urticaria) and Scoring Atopic Dermatitis (SCORAD) index (scores of <25 indicating mild disease, 25-50 moderate disease, and >50 severe disease) were used as the standard scales to grade disease severity.[6,7]

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM SPSS v. 20.0 (IBM Corp., Armonk, NY, USA). The power analysis was performed using G Power 3.1 Manual (Heinrich-Heine-Universitat Düsseldorf, Düsseldorf, Germany). According to basophil counts reported by a previous study; the required study population size was calculated to be 36 patients per group (a=0.05, effect size=0.598, and the study power=0.80).[8] The normality of the data distribution was analyzed by the Shapiro-Wilk test. Non-parametric continuous variables were presented as median (25-75 percentile). Categorical variables were presented as frequency and percent. The differences between the groups were analyzed by the Mann-Whitney U test for numerical variables that did not conform to a normal distribution. Chi-square tests were used to compare SPT results between 2 groups. The relationship between numerical variables was evaluated using Pearson's and Spearman's correlation analyses. Statistical significance was set at $p<0.05$.

RESULTS

Of the 68 patients included in the study, 35 (51.5%) were diagnosed with CSU and 33 (48.5%) were diagnosed with AD. Of the CSU patients, 23 (65.7%) were women and 12 (34.3%) were men. Of the AD patients, 21 (63.6%) were women and 12 (36.4%) were men. The mean age was 37.6±13.22 years in the CSU group and 29.63±10.20 years in the AD group.

The mean disease duration was 11 months in the AD group and 24 months in the CSU group. A statistically significant difference in disease duration was found between the 2 groups ($p=0.011$, $p<0.05$). Total IgE levels were >100 IU/mL (N 0-100 IU/mL) in 34 patients, of which 16 were AD and 18 were CSU patients. The mean basophil and eosinophil counts were 0.10/µL (N 0-0.2 µL) and 0.20/µL (N 0-0.4 µL) in the AD group and 0.00/µL and 0.17 /µL in the CSU group, respectively ($p=0.22$, $p=0.003$, $p<0.05$, respectively). Basophil counts were not statistically significantly different but there was a statistically significant difference in eosinophil counts between the 2 groups ($p=0.003$). The mean SCORAD score was 42.8 (N 0-50) in the AD group and the mean UAS7 score was 28 (N 0-42) in the CSU group (Table 1).

The correlation analysis of disease duration, age, basophil counts, eosinophil counts, total IgE levels, and UAS7 scores in the CSU group revealed a statistically significant positive correlation between age and disease duration ($r_s=0.42$, $p=0.01$) and between basophil counts and total IgE levels ($r_s=0.48$, $p=0.003$) (Figure 1, Figure 2). There were not any correlations across other parameters ($p>0.05$).

In the AD group; a statistically negative correlation of disease duration was found with the eosinophil count, total IgE levels, and SCORAD scores ($r_s=-0.354$, $p=0.04$, $r_s=-0.390$, $p=0.02$, $r_s=-0.421$, $p=0.01$, respectively) and there was a statistically negative correlation between age and SCORAD scores ($p=0.01$, $r=-0.412$). There was a statistically positive correlation of disease duration with basophil counts ($p=0.02$), eosinophil counts ($p=0.04$), and total IgE levels ($p=0.02$). In addition, there was a statistically positive correlation between eosinophil counts and SCORAD scores ($r_s=0.68$, $p=0.00$). A statistically negative correlation was found between eosinophil counts and basophil counts ($r_s=-0.55$, $p=0.00$), between basophil counts and total IgE levels ($r_s=-0.37$, $p=0.03$), and between basophil counts and SCORAD scores ($r_s=-0.69$, $p=0.00$). In the AD group, a statistically positive correlation was detected between total IgE values and SCORAD scores ($r_s=0.34$, $p=0.049$).

SPT RESULTS

Mite and grass positivity were detected in both groups. SPT was positive in 45.7% (n=16) and negative in 54.3% (n=19) of the CSU patients. There

TABLE 1: Distribution of demographic characteristics, laboratory results, SPT results, and disease activity scores of patients.

		Atopic dermatitis	Chronic spontaneous urticaria	p value
Number of patients (n, %)		33 (48.5)	35 (51.5)	>0.05
Gender (female/male)		21/12	23/12	>0.05
Age (mean±SD)		29.63±10.20	37.6±13.22	>0.05
Disease duration (months)		11 (10-28)	24 (14-48)	0.01*
Basophil count (/µL) Median (25^{th}-75^{th} percentile)		0.10 (0.00-0.05)	0.00 (0.00-0.03)	0.22
Total IgE (IU/mL)		110 (54.5-238)	77 (37.02-754)	0.90
Eosinophil count (/µL) Median (25^{th}-75^{th} percentile)		0.20 (0.17-0.40)	0.17 (0.10-0.20)	0.003*
Skin prick test result (n/%)	Positive	22 (66.7%)	16 (45.7%)	0.13
	Negative	11 (33.3%)	19 (54.3%)	
Disease activity score (SCORAD, UAS7)		42.8 (36.5-63.4)	28 (21-34.2)	

SPT: Skin prick testing; SD: Standard deviation; SCORAD: Scoring Atopic Dermatitis; UAS7: Urticaria activity scale. * p<0.05

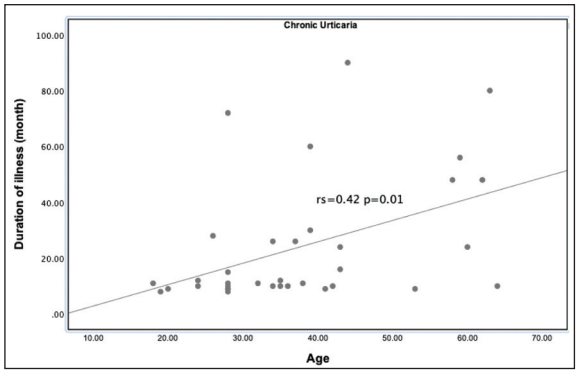

FIGURE 1: A scatterplot graph and bivariate correlation analysis for the age and duration of illness.

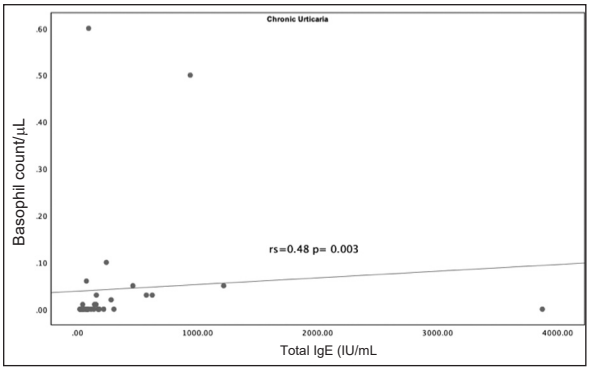

FIGURE 2: A scatterplot graph and bivariate correlation analysis for the total IgE and basophil counts. IgE: Immunoglobulin E.

were no differences in disease duration, eosinophil counts, basophil counts, total IgE levels, and UAS7 scores between CSU patients with positive and negative SPT results (p>0.05).

SPT was positive in 66.7% (n=22) and negative in 33.3% (n=11) of the AD patients. Disease duration was longer in patients with negative SPT results compared to patients with positive SPT results (48-24 months). Total IgE levels were significantly higher in patients with positive SPT results (197 IU/mL) compared to patients with negative SPT results (43.74 IU/mL) (p=0.015). SCORAD scores (50.65) were significantly higher in patients with positive SPT results compared to patients with negative SPT results (37.65) (p=0.004). There were no correlations of eosinophil or basophil counts with SPT results.

DISCUSSION

In this study; we investigated serum levels of total IgE and eosinophil and basophil counts in adult patients with AD and CSU to assess a potential relationship across such biomarkers, SPT results, and disease severity, and we aimed to clarify discrepancies in results reported by previous studies.

Hypersensitivity reactions associated with IgE are categorized into early-stage and late-stage reactions.[8] Mast cells and basophils are defined as the cells responsible for early hypersensitivity reactions. Eosinophils are defined as the cells responsible for late-stage reactions.[9]

Eosinophils are active pro-inflammatory cells that trigger AD pathogenesis by activating the

eosinophil cationic protein, major basic protein-1-2, eosinophil-mediated neurotoxins, and basophils and mast cells, and by increasing the synthesis of cytokines such as IL-12, IL-13, IL-16, and transforming growth factor beta; all of which are released from the granules inside eosinophils taking an important part in the pathogenesis of allergic diseases.[10] These mechanisms support the relationship between elevated eosinophil counts and AD disease severity. Hypereosinophilia and elevated serum IgE levels are the most common laboratory findings in AD.[11] In our study, too, consistent with the information in the literature; we found a statistically significant increase in eosinophil counts in the AD group in parallel to the increase in SCORAD scores as indicators of disease activity.

Warner et al found that disease severity was proportional to total IgE levels in children with AD.[12] Hon et al. have reported that age-specific IgE is proportional to disease activity.[13] Another study has reported that the disease severity of AD and elevations in IgE levels are correlated.[14] Wu et al. have reported a correlation between total IgE levels and SCORAD index in children with AD.[15] A significant association between allergen-specific IgE and disease severity has been reported in 2,201 children aged 5-14 with AD.[16] A study on 80 adult AD patients from Brazil has shown that disease severity is associated with higher serum total IgE levels and blood eosinophil counts.[17] Hu et al. have reported that total IgE levels and eosinophilia correlate with AD disease severity index.[18] In our study; consistent with the information in the literature, we found increases in both total IgE levels and serum eosinophil counts as the disease activity score (SCORAD) increased. Basophil counts, on the other hand, were negatively correlated with SCORAD index scores and total IgE levels. These findings indicate that eosinophil counts and total IgE levels are more prominent in acute exacerbations in AD and basophil counts increase in the chronic period.

Kiiski et al. also reported that having low total IgE levels was an important criterion in determining the treatment response and the long-term remission success in AD.[19] Therefore, it is recommended that total IgE levels should be monitored as an inexpensive and easy method and an important biomarker to follow up the disease course in AD and to identify AD patients needing to be followed up closely. In our study; similar to the study of Kiiski et al, total IgE values increased as SCORAD scores increased and these values were significantly higher in AD patients with positive SPT results compared to patients with negative SPT results. Flohr et al. have reported that AD severity is correlated by positive SPT results and high IgE levels.[20] In light of these findings, we think that monitoring total IgE values is a more practical option in clinical practice to follow up the disease course despite predicting SPT positivity, total IgE level elevations, and high SCORAD scores are predicted in acute AD.

IgE is the primary mediator in the Type-1 hypersensitivity response and is responsible for the early immune response. In the etiopathogenesis of urticaria, it is thought that free IgEs bind to FcεRI and cause histamine release from mast cells. Expressing various membrane receptors, eosinophils sensitize such receptors to a variety of molecules and cause the release of pro-inflammatory mediators. Thus; eosinophils, just as basophils and mast cells might be activated by allergens via cross-linking of cell-surface-bound IgEs in allergic CSU.[21]

It is thought that eosinophils are involved in the late stages of urticaria and act as the main cells, especially, responsible for the occurrence of severe cases of urticaria resistant to antihistamines.[22] Eosinophils increase vascular permeability and stimulate histamine release from mast cells by stimulating the coagulation pathway.[23] It has been shown that eosinophil counts in the peripheral blood decline and eosinophil counts increase in tissues in CSU.[24] In the pathogenesis of CSU, cationic proteins are released from the granules inside eosinophils through the degranulation of eosinophils that are activated by cytokines such as IL-2, IL-4, IL-10, and interferon gamma released in the inflammatory pathway. Then, eosinophils start accumulating in the dermis and become involved in the development of urticaria lesions. Consequently, eosinophil counts decrease in the peripheral blood.[21]

Altricher et al, have reported that eosinopenia is seen in a subpopulation of patients with urticaria, especially in urticaria cases, where autoimmune mechanisms are responsible. Altricher et al, have also reported that, in chronic spontaneous urticaria, eosinopenia is linked to high disease activity, autoimmunity, and poor response to treatment.[25] In our study; compared to AD patients, eosinophil counts were lower in patients with CSU ($p=0.003$, $p<0.05$) and there was not a statistically significant correlation between eosinophil counts and disease activity in the CSU group.

Chang et al, and Kessel et al, have reported that total IgE is high in CSU and correlated with disease activity.[26,27] In a study by Baek et al, it has been reported that the severity of urticaria is not associated with C reactive protein and total IgE levels but urticaria severity is consistent with D-dimer levels.[28] In our study, no correlations of disease activity severity (UAS7) were found out with eosinophil and basophil counts and total IgE levels in the CSU group. In addition, no correlations of SPT results were observed with these parameters.

In some studies, basophenia has been reported in the peripheral blood in acute urticaria and it has been reported that blood basophil counts are found elevated in remission when the disease activity scores improve, in other words, decrease.[29] de Montjoye et al, have reported that basophil levels are lower in CSU patients compared to healthy individuals and that a negative correlation is observed between disease activity and basophil counts.[30] It has been emphasized that the serum basophil count decreases as a result of the migration of circulating basophils to urticarial plaques in parallel to increased disease activity in urticaria.[31] In our study, too, we found decreased basophil counts in parallel to decreased total IgE levels in the CSU group. We think that the occurrence of these results may be related to the examination of urticaria patients in the chronic period.

However, Kolkhir et al, reported that 10% of CSU patients had eosinopenia and basophenia and that patients with low blood eosinophil counts had higher urticaria disease severity, responding poorly to omalizumab therapy.[32] In our study, no relationships were found between disease activity scores and basophil counts in CSU patients but basophil counts were found to have increased as total IgE levels increased. Furthermore, it was observed that UAS scores were independent of both total IgE levels and levels of other laboratory parameters.

Wong et al, have reported in a review of 2,982 patients with CSU that the SPT positivity with high IgE levels is most commonly found against aeroallergens.[33] Chang et al, have found out that sensitization develops most commonly to aeroallergens in acute and CSU.[26] Oncham et al, have found out that mite sensitization was most common in SPT in AD and CSU patients.[34] Bains et al, found SPT positivity in their study at rates of 63.41% and 77.78% in the CSU and AD patient groups, respectively. In addition, dust and pollen were the most common allergens in the group with urticaria and grain dust wheat was the most common allergen in the group with AD.[35] In our study, SPT was positive in 45.7% of the CSU patients and 66.7% of the AD patients and the prick test positivity was higher in the AD group. However, SPT results were not significantly different between the groups. Of the identified allergens, positivity to mites predominated in both groups.

CONCLUSION

In our study, serum parameters and disease activity scores were compared and SPT results were evaluated in patients with CSU and AD. In conclusion, we think that monitoring the disease activity with serum IgE and eosinophil levels is sensible in AD but following up the levels of serum parameters is not sensible in CSU.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Yeşim Akpınar Kara;* ***Design:*** *Yeşim Akpınar Kara;* ***Control/Supervision:*** *Yeşim Akpınar Kara, Hatice Kaya Özden;* ***Data Collection and/or Processing:*** *Yeşim Akpınar Kara, Hatice Kaya Özden;* **Analysis and/or Interpretation:** *Yeşim Akpınar Kara, Hatice Kaya Özden;* ***Literature Review:*** *Yeşim Akpınar Kara, Hatice Kaya Özden;* ***Writing the Article:*** *Yeşim Akpınar Kara, Hatice Kaya Özden;* ***Critical Review:*** *Yeşim Akpınar Kara, Hatice Kaya Özden;* ***References and Fundings:*** *Yeşim Akpınar Kara, Hatice Kaya Özden.*

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