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The Effect of Diet on ECP, IL-4 and IL-31 in Patients with Persistent Allergic Rhinitis

Persistan Alerjik Rinitli Hastalarda Diyetin ECP, IL-4 ve IL-31 Üzerine Etkisi

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ABSTRACT

Objective: The aim of this study is to evaluate the effects of dietary changes on late phase of allergic reaction in patients with allergic rhinitis (AR) by measuring eosinophilic cationic protein (ECP), interleukin (IL)-4 and IL-31 levels.

Methods: Sixty participants (40 patients with AR and 20 healthy control subjects) were included in this study. Forty patients with confirmed diagnosis of AR were randomly divided into two groups, all patients were prescribed the same treatment, intranasal azelastine hydrochloride. Patients in group 1 were asked to change their diet from Western to Mediterranean diet by eliminating processed meat, processed sugar, and polyunsaturated fatty acids. Blood samples of every subject were driven at the beginning and three months later to study ECP, IL-4 and IL- 31 levels. By using ELISA method IL-4 and IL-31 levels were determined and compared between healthy volunteers and patients.

Results: There was a significant difference in terms of ECP levels in group 2. The posttreatment ECP levels were significantly higher than pretreatment levels in group 2 ($p=0.025$ and $p<0.05$). There was no significant difference in terms of other parameters.

Conclusion: In our study, we showed that the laboratory parameters associated with AR were positively affected by the Mediterranean diet.

Keywords: Allergic rhinitis, diet, eosinophil cationic protein, interleukin-4, interleukin-31

ÖZ

Amaç: Bu çalışmanın amacı, alerjik rinitli (AR) hastalarda diyet değişikliklerinin alerjik reaksiyonun geç fazındaki etkilerini eozinofilik katyonik protein (ECP), interlökin (IL)-4 ve IL-31 düzeylerini ölçerek değerlendirmektir.

Yöntemler: Bu çalışmaya 60 katılımcı (AR'li 40 hasta ve kontrol grubuna 20 sağlıklı birey) dahil edildi. AR tanısı doğrulanmış 40 hasta rastgele iki gruba ayrıldı, tüm hastalara aynı tedavi, intranazal azelastin hidroklorür, verildi. Grup 1 hastalarına diyetlerinden işlenmiş et, işlenmiş şeker ve çoklu doymamış yağ asitlerini ortadan kaldırarak Akdeniz tipi beslenmeye uygun beslenmeleri söylendi. Her denekten ECP, IL-4 ve IL-31 düzeylerinin ölçülmesi için başlangıçta ve üç ay sonra kan örneği alındı. Elde edilen veriler istatistiksel olarak incelendi.

Bulgular: Grup 2'de ECP düzeylerine göre anlamlı bir fark saptandı. Grup 2'de tedavi sonrası ECP düzeyleri tedavi öncesi değerlere göre anlamlı derecede yüksekti ($p=0,025$ ve $p<0,05$). Diğer parametreler açısından anlamlı bir fark yoktu ($p>0,05$).

Sonuç: Çalışmamızda AR ile ilişkili laboratuvar parametrelerinin Akdeniz diyetinden olumlu yönde etkilendiğini gösterdik.

Anahtar kelimeler: Alerjik rinit, diyet, eosinofil katyonik protein, interlökin-4, interlökin-31

INTRODUCTION

Allergic rhinitis (AR) is a common nasal inflammatory disease characterized by runny nose, itching and nasal congestion (1). AR is categorized as intermittent or persistent according to the frequency and duration of symptoms (2). AR, which is accepted as the most common chronic disease in children by the World Health Organization, affects 10-30% of children in developed countries and its prevalence has increased worldwide, especially in industrialized countries (3-5). It has been hypothesized that a change in lifestyle, especially dietary habits, is considered as an important factor of AR development (4).

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AR is chronic inflammatory disease of nasal airway. Imbalance in T helper 1 (Th1)/T helper 2 (Th2) response is responsible for this allergic reaction (6). Eosinophils and released mediators promote Th2 maturation and shift in response contributes to AR (7). Eosinophils and mediators localized in their granules such as eosinophilic cationic protein (ECP) are effectors in allergic reactions such as AR (8,9). ECP has been measured in body fluids, including serum, and nasal secretions of patients with allergic and other inflammatory diseases (10).

One of the key cytokines in Th2 maturation and shifting is IL-4. IL-4's receptor shares same receptor subunit with IL-13 receptor which induces IgE isotype switching, T-cell population shifts to Th2 cell (11,12). IL-4 also promotes eosinophils and Th2 migration to the inflammatory site (13). In addition to these effects, it has been reported that IL-31 is produced by many cell groups in the presence of IL-4, and this triggers Th2-mediated inflammation (14). It is thought that IL-31 is produced by many cell groups in the presence of IL-4, and this triggers Th2-mediated inflammation (14).

The IL-31 is another effector cytokine of Th2. It plays important role in the pathogenesis of atopic and allergic diseases. IL-31 is released from activated Th2 cells (15). Antigen-induced IL-31 production in the AR process has a special and independent role in the pathophysiology of AR, unlike other Th2 cytokines such as IL-5 and IL-13 (16).

Environmental exposures, climate changes and lifestyle are important risk factors for AR. Many hypotheses are considered for the development of allergies. One of these hypotheses is the triggering effect of allergic inflammation of the Western diet (WD), which is rich in antioxidants and rich in polyunsaturated fatty acids (17). It is hypothesized that increased consumption of high protein and fatty foods and processed dairy products and less consumption of fresh fruits, vegetables and whole grains in the WD contribute to AR (18). Mediterranean diet (MD) is characterized by high intake of fruit, vegetables, fish and olive oil (19). It is characterized with balanced ratio of n-6/n-3 essential fatty acids, fiber, antioxidants and monounsaturated fatty acids and anti-oxidants such as fresh fruits and vegetables (20,21). It is hypothesized to have a protective effect on chronic inflammatory airway diseases such as asthma and AR (22-24).

In this study, the effects of removing trans fatty acids, milk, and dairy products from the diets of patients diagnosed as having persistent AR by prick test, that is, converting a WD to a MD, on serum IL-4, IL-31 and ECP levels were evaluated.

METHODS

This study was conducted prospectively on patients and volunteers who were admitted to Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Ear Nose Throat Department's Allergy Clinic with the approval of Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (no: 83045809/18849, date: 12.07.2013).

Forty patients with AR were included in this study. Informed consent form was obtained from each subject or subject's custodian for under aged subjects. All patients were questioned for allergic symptoms, endoscopic nasal examinations were performed, and skin prick tests were planned. The skin prick test (Multi Test®, Lincoln Diagnostics Ltd, USA) was performed according to European Academy of Allergology and Clinical Immunology guidelines to support the diagnosis of allergy and to determine the allergen or allergens in the etiology of the disease.

The exclusion criteria were as follows: lack of mental capacity, history of anaphylaxis, being diagnosed as having vasomotor rhinitis or non-AR, having any other positive allergic reaction on prick test, presence of a chronic disease, use of any medication, alcohol dependence and smoking, and refusing to participate in the study. Considering these criteria, 40 patients, with allergic symptoms and positive prick test only for house dust mite Dermatophagoides farinea and/or Dermatophagoides pyteronysinus, were included in the study. The control group was composed of 20 healthy individuals aged 18 to 49 years with negative prick test.

Patients were randomly divided into two groups. Patients in group 1 were prescribed azelastine hydrochloride two times daily and given a list that contained banned and allowed foods and a check list to mark the progress each day. Dairy products, processed sugar and trans fatty acid consumptions were restricted. Group 2 was only prescribed azelastine hydrochloride twice a day and it was stated that they could eat whatever they wanted. The control group was named as group 3.

A full ENT examination was performed every month for each patient and the diet check lists of the patients in group 1 were controlled. Five cc of venous blood was collected from all patients at the beginning of the study (Day 0) and at third month (3rd Month) for measuring ECP, IL-4 and IL-31 levels, and restored in a -70 °C refrigerator. Control group's blood samples were only collected at the beginning to measure IL-4 and IL-31 levels. ECP was not allergy specific and therefore it was not studied in the control group (9,10).

ECP

Blood samples from each patient were collected in anti-coagulant free tube by the same nurse, tubes were slowly turned upside down for 5 times, restored 1-2 hours at the room temperature, then studied in the laboratory.

ELISA Detection Method

Human IL-4 ELISA Kit Diaclone® (France) and Human IL-31 ELISA Kit Diaclone® (France) were used to determine the concentration of IL-4 and IL-31 levels in serum samples. Standard and samples were read with 450 nm reading filter and linear regression analysis was used to calculate results.

Statistical Analysis

Statistical analysis was performed with SPSS Version 21.0 (SPSS Inc., USA) program. It was evaluated whether the groups showed

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normal distribution by Kolmogorov-Smirnov test. Homogeneity of variances was evaluated by Levene test. The values of the parameters in groups at the beginning and the end of the research were analyzed with Wilcoxon signed-ranks test. The comparison between the groups was performed with the Kruskal-Wallis test. Paired comparison of groups was performed with Mann-Whitney U test. Bonferroni correction was used to counteract the multiple comparisons problem. The significance level was accepted as $p<0.05$. The significance level for Mann-Whitney U test with Bonferroni correction was accepted as $p<0.025$.

RESULTS

Twenty-three of 40 patients (57.5%) were female, and 17 of 40 patients (42.5%) were male. Group 1 had 9 (45%) female 11 (55%) male patients, mean age was 18.95±9.16, and range was 6-36 years. Group 2 had 14 (70%) female, 6 (30%) male patients, mean age was 22.58±9.19, and range was 8-36 years.

The ECP levels of group 1 and 2 and their comparisons were given in Table 1. In the evaluation made in terms of the ECP levels, a statistically significant difference was found between the beginning of the research and the end of the 3rd month in group 2 (p=0.025). In other comparisons made in terms of ECP values, no statistically significant difference was found in the groups (p>0.05) (Table 1).

IL-4 levels of groups were given in Table 2. A statistically significant difference was found between the groups in terms of the IL-4 values at the beginning of the research (p=0.001 and p=0.001, respectively). In paired comparison of the groups, IL-4 levels in group 1 and 2 were found to be statistically significantly higher than the control group at the beginning (p=0.001 and p=0.001, respectively). However no statistically significant difference was found in the comparison between patient groups (p=0.704). And also, a statistically significant difference was found between the patient and control groups in terms of the IL-4 levels at the end of the research (p=0.001 and p=0.001, respectively). In paired comparison of the groups, IL-4 levels in both group 1 and 2 were found to be statistically significantly higher than the control group at the end of the research (p=0.001 and p=0.001, respectively). However, no statistically significant difference was found in the comparison between patient groups (p=0.913). There was no statistically significant difference between the patient groups in the comparison made in terms of the initial and final IL-4 levels (p=0.925 and p=0.432, respectively) (Table 2, 3).

The IL-31 levels of groups were given in Table 2. A statistically significant difference was found between the patient and control groups in terms of the IL-31 levels at the beginning of the research (p=0.001). In paired comparison of the groups, IL-31 levels in both group 1, 2 were found to be statistically significantly higher than the control group at the beginning (p=0.001 and p=0.001, respectively). However, no statistically significant difference was found in the comparison between patient groups (p=0.542). And a statistically significant difference was found between the patient and control groups in terms of the IL-31 levels at the end of the research (p=0.125). In paired comparison of the groups, IL-31 levels in both group 1 and 2 were found to be statistically significantly higher than the control group at the end (p=0.001 and p=0.001, respectively). However no statistically significant difference was found in the comparison between patient groups (p=0.125). There was no statistically significant difference in both groups in the comparison made in terms of the initial and final IL-31 levels (p=0.709 and p=0.341, respectively) (Table 3, 4).

DISCUSSION

AR is one of the most common allergic diseases (1). In addition to genetic predisposition, many environmental factors have an effect on this disease (17). One of these factors is eating habits (17). In this study, we applied a MD in addition to local

Table 1. Comparison of ECP levels between groups and between months

ECP	Before treatment day 0 Median (min-max)	After treatment 3rd month Median (min-max)	p*
Group 1 (n=20) (µg/L)	48.75 (5.48-108)	59.95 (13.3-152)	0.179
Group 2 (n=20) (µg/L)	32.6 (4.56-90.8)	49.65 (18-201)	0.025
p**	0.138	0.433	

ECP: eosinophilic cationic protein, min: minimum, max: maximum, *Wilcoxon signed-ranks test p<0.05, **Mann-Whitney U test with Bonferroni Correction p<0.025

Table 2. Comparison of groups according to IL-4 levels

IL-4	Day 0 Median (min-max)	3rd month median (min-max)	p**
Group 1 (n=20) (pg/mL)	0.41 (0.04-2.04)	0.38 (0.17-2.03)	0.925
Group 2 (n=20) (pg/mL)	0.34 (0.14-0.73)	0.38 (0.18-1.46)	0.432
Group 3 (n=20) (pg/mL)	0.2 (0.18-0.31)		
p*	0.001	0.001	

*Kruskal-Wallis test p<0.05, **Wilcoxon signed-ranks test p<0.05, min: minimum, max: maximum, IL: interleukin

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Table 3. Statistical evaluation of interleukin levels

	Compared groups	IL-4		IL-31	
		Day 0	3rd month	Day 0	3rd month
p*	1-2	0.704	0.913	0.542	0.125
	1-3	0.001	0.001	0.001	0.001
	2-3	0.001	0.001	0.001	0.001

*Mann-Whitney U test with Bonferroni correction p<0.025

Table 4. Comparison of groups according to IL-31 levels

IL-31	Day 0 Median (min-max)	3rd month Median (min-max)	p**
Group 1 (n=20) (pg/mL)	21.2 (0.19-138)	21.4 (0.19-81.4)	0.709
Group 2 (n=20) (pg/mL)	18.74 (0.19-85)	18.74 (0.19-100)	0.341
Group 3 (n=20) (pg/mL)	3.1 (0.2-7.5)		
p*	0.001	0.001	

*Kruskal-Wallis test p<0.05, **Wilcoxon signed-ranks test, IL: interleukin, min: minimum, max: maximum

treatment in patients with AR. As a result, there was no significant increase in ECP level, which was an indicator of systemic inflammation, at the end of the study in the group fed with MD, while a significant increase was observed in the free-fed group (p=0.025). In addition, IL-4 level, which had an important role in the inflammation mechanism due to AR, decreased in the MD group, while an increase was observed in the free-fed group. However, this change was not statistically significant (p=0.925). There was no significant difference in terms of IL-4 levels between the two patient groups after treatment (p=0.913). Although IL-31 level, which was involved in the pathogenesis of AR and was associated with disease severity, decreased in both groups, and this decrease was not significant (p=0.709 and p=0.341, respectively). There was no significant difference in terms of IL-31 levels between the two patient groups after treatment (p=0.125).

Turkey is geographically located in the easternmost part of the MD belt. However, in parallel with the socio-cultural life in Turkey, of which integration with the West is increasing, it has begun to shift to WD. We planned this study to examine the possible effects of this change on patients with AR. Since nutrition was a physiological event with systemic effects, we chose local treatment to minimize the systemic effects of AR with the treatment we would give, and for the same reason, we used azelastine hydrochloride, an antihistamine, locally, instead of corticosteroids. ECP is the major protein in AR and its serum levels correlate with AR (10,25). IL-4 and IL-31 are involved in the pathophysiology of AR (16,26,27). IL-31 levels also correlate with the severity of the AR clinic (28,29). By determining the levels of these markers, we aimed to determine both the effect of nutrition on the inflammatory process associated with AR and the possible effect on the clinical severity of AR.

Eosinophils are cells that are at the center of allergic reactions. ECP is secreted from the granules in these cells in the last phase of allergic reactions, and the ECP level is higher in patients with AR than in non-allergic patients and shows a positive correlation with AR (8-10,25). In our study, ECP levels increased during the study period in both patient groups, probably due to the fact that a systemic anti-allergic treatment was not used. However, while this increase was statistically significant in the free-fed group (p=0.025), no significant increase was observed in the Mediterranean-type fed patients. This result may show us that the MD reduces inflammation associated with AR.

The IL-4 is involved in the development and maintenance of allergic inflammation seen in airway mucosa of patients with allergic respiratory disorders, such as AR (30,31). IL-4 plays a critical role in the pathogenesis of AR, especially in the late phase of the disease (32). While the level of this marker, which was directly related to inflammation in AR, increased in the free-fed group in our study, it decreased in the Mediterranean-type fed patient group. This result can be interpreted that MD reduces allergic inflammation.

The IL-31 levels increase in AR and its levels correlate with the clinical severity of the disease (33). No significant difference was found in the statistical analyzes of IL-31, which was the marker most closely associated with the AR clinic among the laboratory parameters we examined in our study. This can be explained by the small number of patients and the short study period.

Study Limitations

There were some limitations of this study, in which we examined the relationship between MD and laboratory parameters of AR. The first of these was that we determined a short study period of 3 months to evaluate the parameters of AR, which was a chronic disease. The shortness of this period was in order to ensure the compliance of the patients with the diet. Our most important limitation was the small number of patients included in our study. This was because our budget was limited for the kits we used for laboratory evaluation.

CONCLUSION

AR is one of the most common chronic allergic diseases. This disease, which is affected by many environmental factors, may also be affected by the type of nutrition. As a result of our study, we determined that the laboratory parameters associated with AR were positively affected by the MD. Based on the results of our study, we may say that WD may negatively affect AR, while MD may reduce inflammation of AR and severity of AR.

Ethics Committee Approval: This study was approved by the Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (no: 83045809/18849, date: 12.07.2013).

Informed Consent: Informed consent form was obtained from each subject or subject's custodian for under aged subjects.

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