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ORIGINAL ARTICLE

Serum interleukin-36γ levels in children with allergic rhinitis: a cross-sectional study

Niveles séricos de interleucina-36γ en niños con rinitis alérgica: un estudio transversal

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Allergic rhinitis, pediatric allergy, disease severity, cytokines, IL-36γ

Palabras clave
Rinitis alérgica, alergia pediátrica, disease severity, citocinas, IL-36γ

Remark

1) Why was this study conducted?

This study aimed to investigate whether serum Interleukin 36 gamma (IL-36γ) levels in pediatric allergic rhinitis patients correlate with disease severity (mild, moderate, severe) and duration (intermittent, persistent).

2) What were the most relevant results of the study?

IL-36γ levels were higher in the patient group with borderline significance (p= 0.050). Female patients had significantly higher IL-36γ levels than male controls (p= 0.044).

3) What do these results contribute?

This is the first study to evaluate IL-36γ levels in pediatric allergic rhinitis. Although the difference between groups showed borderline significance, larger studies may confirm these findings. The observed gender-related difference suggests IL-36γ could be a potential biomarker. Future prospective studies with larger sample sizes should investigate IL-36γ in pediatric allergic rhinitis, considering sex-related differences, to determine its clinical utility in assessing disease severity and guiding management.

Conflict of interest

The authors declare that they had no conflict of interest during the preparation and publication of this study

Funding:

The authors declare that the cost of IL-36 ELISA kits was covered by the Scientific Research Budget of the SBU Antalya Training and Research Hospital as part of a medical specialization thesis project.

Authors contributions:

Dogukan Aydenizoz, conceptualization, data curation, formal analysis, resources, software, supervision, validation, visualization, writing, original draft writing, review & editing; Omer Tarik Selcuk, funding acquisition, investigation, methodology, project administration, review & editing; Hulya Eyigor. formal analysis, resources, software, supervision, validation, visualization writing, Hamit Yasar Ellidag, conceptualization, data curation, formal analysis, funding acquisition, investigation; Serkan Filiz, formal analysis, resources, software, investigation, methodology, project administration; Sennur Keles, data curation, formal analysis, resources, software, supervision, validation, visualization, writing, original draft writing, review & editing

Data Availability

The authors confirm that the data supporting the findings of this study are available in the article and/or its supplementary materials

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Abstract

Objectives:

This study aimed to investigate whether serum Interleukin 36 gamma (IL-36γ) levels in pediatric allergic rhinitis patients correlate with disease severity (mild, moderate, severe) and duration (intermittent, persistent). Additionally, we assessed the potential of IL-36γ as a biomarker and its role in disease pathogenesis to inform future treatment strategies.

Methods:

In this cross-sectional observational study, pediatric allergic rhinitis patients from outpatient clinics were compared with healthy controls. Serum IL-36γ levels were measured from blood samples and analyzed across subgroups based on disease severity and duration.

Results:

Fifty patients with allergic rhinitis and forty controls were included. IL-36γ levels were higher in the patient group with borderline significance (p= 0.050). Female patients had significantly higher IL-36γ levels than male controls (p= 0.044).

Conclusions:

This is the first study to evaluate IL-36γ levels in pediatric allergic rhinitis. Although the difference between groups showed borderline significance, larger studies may confirm these findings. The observed gender-related difference suggests IL-36γ could be a potential biomarker. Additionally, a significant negative correlation with total IgE and a nonsignificant negative correlation with eosinophil counts were noted.

Resumen

Objetivos:

Investigar si los niveles séricos de interleucina 36 gamma (IL-36γ) en pacientes pediátricos con rinitis alérgica se correlacionan con la gravedad de la enfermedad (leve, moderada, grave) y su duración (intermitente, persistente). Además, evaluamos el potencial de la IL-36γ como biomarcador y su papel en la patogénesis de la enfermedad para implementar futuras estrategias de tratamiento.

Métodos:

En este estudio observacional transversal, se comparó a pacientes pediátricos con rinitis alérgica de clínicas ambulatorias con controles sanos. Se midieron los niveles séricos de IL-36γ a partir de muestras de sangre y se analizaron en subgrupos según la gravedad y la duración de la enfermedad.

Resultados:

Se incluyeron 50 pacientes con rinitis alérgica y 40 controles. Los niveles de IL-36γ fueron más altos en el grupo de pacientes, con una significación límite (p= 0.050). Las pacientes mujeres tenían niveles de IL-36γ significativamente más altos que los controles masculinos (p= 0.044).

Conclusiones:

Este es el primer estudio que evalúa los niveles de IL-36γ en la rinitis alérgica pediátrica. Aunque la diferencia entre los grupos mostró una significación límite, estudios más amplios podrían confirmar estos hallazgos. La diferencia observada en función del sexo sugiere que la IL-36γ podría ser un posible biomarcador. Además, se observó una correlación negativa significativa con la IgE total y una correlación negativa no significativa con el recuento de eosinófilos.

Introduction

Allergic rhinitis is a common global public health problem, with a prevalence ranging from 2-25% in children and 1-40% in adults and is estimated to affect approximately 500 million individuals worldwide [1]. The clinical presentation is characterized by nasal congestion, rhinorrhea, and sneezing [2].

Allergic rhinitis is characterized by chronic mucosal inflammation induced by an IgE-mediated type I hypersensitivity reaction. This reaction is triggered by inflammatory mediators released after antigen presentation, T-cell proliferation, IgE synthesis, and mast cell degranulation. In type I hypersensitivity reactions, IgE molecules are activated when an allergen binds to the surface of tissue mast cells and basophils. This leads to immune dysregulation mediated by T helper 2 (Th2) cells in the upper respiratory tract mucosa, resulting in eosinophil-dominated inflammation and the development of allergic rhinitis. Many individuals develop allergies due to type I hypersensitivity, also known as atopic allergy. Among allergic diseases caused by type I hypersensitivity, allergic rhinitis is the most common [3-5]. The ARIA guidelines classify allergic rhinitis according to both symptom frequency (intermittent or persistent) and disease severity (mild, moderate, or severe) [1,6].

The interleukin-36 (IL-36) group belongs to the interleukin-1 cytokine family and includes IL-36α, IL-36β, IL-36γ, and the IL-36 receptor antagonist. Monocytes/macrophages, T cells, neurons, keratinocytes, and respiratory epithelial cells can secrete IL-36. Although the molecular mechanisms by which the IL-36 family contributes to allergic rhinitis are not clearly understood, these cytokines are believed to play an important role in regulating inflammation. Although studies investigating the role of IL-36 cytokines in allergic rhinitis are limited, previous research has reported significantly higher serum IL-36, IL-36β, IL-36γ, IL-36Ra, and IL-36R levels in allergic rhinitis patients compared with healthy controls, with IL-36γ showing the highest levels among them [7-10].

The objective of the present study was to evaluate the relationship between serum IL-36γ levels and disease severity and duration in pediatric allergic rhinitis patients, and to determine the potential utility of serum IL-36γ as a biomarker in this population.

Materials and Methods

Study group

The patient group in this study consisted of 50 children diagnosed with allergic rhinitis between February 1, 2021 and March 1, 2022, at the Otorhinolaryngology and Pediatric Allergy and Immunology outpatient clinics of the Health Sciences University Antalya Training and Research Hospital. Diagnosis was based on clinical history, physical examination, skin prick testing, and serum total and specific IgE measurements. None of the patients had a history of asthma, chronic urticaria, or any other allergic disease. Clinical findings, visual analogue scale (VAS) scores, nasal obstruction symptom evaluation scale (T-NOSE) scores, disease severity and duration, demographic characteristics, height, weight, body mass index, family history of allergy, exposure to passive smoking, and contact with animals were recorded. Patients who volunteered to participate provided informed consent before enrollment.

The control group comprised children who attended the Otorhinolaryngology and Pediatric Allergy and Immunology outpatient clinics of the same hospital, selected randomly without any history of allergic disease, asthma, chronic urticaria, or acute illness, and who presented non-specific complaints. No matching criteria were applied when selecting the control group (Figure 1).

For both groups, 5 mL of peripheral blood was collected into EDTA biochemistry tubes and stored at +4 °C until analysis. All samples were processed in the same central biochemistry laboratory. In addition to IL-36γ measurement, routinely requested pediatric allergy and

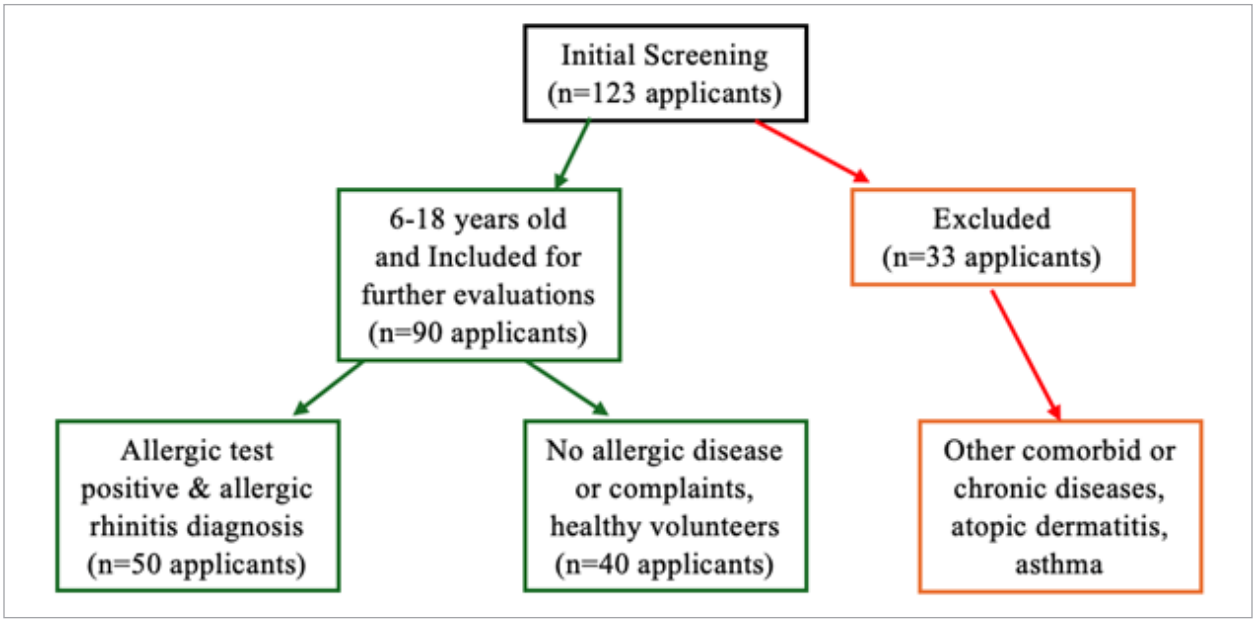

Figure 1. Flowchart of Inclusions and Exclusions

immunology laboratory parameters (leukocyte count, eosinophil count and percentage, C-reactive protein (CRP), erythrocyte sedimentation rate, total IgE, and serum specific IgE values) were recorded.

In this cross-sectional observational study, the sample size was calculated using G*Power 3.1.9. The effect size was determined as d= 0.68. For 95% statistical power and a 0.05 margin of error, the minimum sample size required was calculated as 90 in total: 50 in the study group and 40 in the control group.

Criteria for inclusion. Patients between the ages of 6-18 who were diagnosed with allergic rhinitis and whose disease degree was classified as mild, moderate and severe according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline.

Criteria for exclusion. Patients over 18 years of age; those diagnosed with rhinitis medicamentosa, psychiatric disorders, malignancy, chronic or comorbid diseases; and those with atopic dermatitis, asthma, or chronic urticaria.

Compliance with ethical standards. Approval for the study was granted by the Ethics Committee of Antalya Training and Research Hospital (2020-19/9), and informed consent was obtained from all individual participants for whom identifying information is included in this article.

Interleukin 36 Gamma serum level detection

Peripheral blood samples from volunteers participating in the study, SBU. It was studied with the help of the ELISA (Enzyme Linked Immune Absorption Assay) device (ETI Max 300, DİaSorin S.p.A., Saluggia, Italy, 2015) located in the Biochemistry Laboratory of Antalya Training and Research Hospital. The ELISA kits used are Human IL-36γ ELISA Kit (AFG Bioscience) for the quantitative level of Human IL-36γ in serum samples, adopting purified IL-36γ antibody to coat the microtiter plate, make a solid phase antibody, and then add IL-36γ to the wells. By adding 36γ, it combines the IL-36γ antibody with the labeled HRP. Antibody-antigen enzyme-antibody complexes are formed. After complete washing, the TMB substrate is dissolved. In the presence of HRP enzyme, the TMB substrate turns blue. The reaction is terminated by adding a stop solution, which works by making color changes at a wavelength of 450 nm. Detection range: 2pg/

ml-80 pg/ml, sensitivity 0.85 pg/ml, 96 test kits. Decision programming was made as CV(%)= SD/mean x 100, Intra-Assay: CV <8%, Inter-Assay: CV <10%.

The cost of IL-36 ELISA kits was covered by the Scientific Research Budget of the SBU Antalya Training and Research Hospital as part of a medical specialization thesis project.

This study was approved by the SBU Antalya Training and Research Hospital Scientific Research Ethics Committee on December 10, 2020 (decision no. 19/9). Written informed consent was obtained from all participants and/or their legal guardians. Random sampling was used to minimize selection bias.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for macOS, version 23.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were presented as frequency (n) and percentage (%) and analyzed using Pearson's chi-square test. The Shapiro-Wilk test was used to assess the normality of continuous variables. Normally distributed data were expressed as mean ± standard deviation (SD), while non-normally distributed data were expressed as median interquartile range (IQR), 25th-75th percentile. The independent t-test was used to compare age and body mass index between the allergic rhinitis and control groups. Serum IL-36γ levels between two independent groups were compared using the Mann-Whitney U test. Correlations between serum IL-36γ levels and age, body mass index, IgE, eosinophils, CRP, T-NOSE score, VAS score, and disease duration were evaluated using Spearman's correlation test. A p-value <0.05 was considered statistically significant.

Results

A total of 90 subjects, 50 allergic rhinitis patients and 40 control subjects, were included in the study. The average age of allergic rhinitis patients was 11.58 ±3.81 years, and the control group was 11.78 ±3.17 years. No significant difference was observed in terms of gender distribution and body mass index averages of patients in the allergic rhinitis and control groups (p= 0.887 and p= 0.255). In patients with allergic rhinitis, the rate of family history of atopy (60%) was significantly higher than in the control group (20%) (p <0.001). Demographic information of patients in the allergic rhinitis and control groups is given in Table 1.

Table 1. Demographic data

Variables	Allergic Rhinitis (n= 50)	Control (n= 40)	p
Age (yıl), mean ±SD	11.58 ±3.81	11.78 ±3.17	0.796
Gender, n (%)			
Male	22 (44)	17 (42.5)	0.887
Female	28 (56)	23 (57.5)	
Body mass index (kg/m2), mean ±SD	19.28 ±4.4	20.3 ±3.92	0.255
Atopic family history, n (%)			
No	20 (40)	32 (80)	<0.001
Yes	30 (60)	8 (20)	

Independent t-test, Pearson ki-kare test

The median serum IL-36γ level was 24.76 pg/mL (IQR: 13.42 - 30.67) in the allergic rhinitis group and 16.1 pg/mL (IQR: 8.17 - 24.76) in the control group. Although serum IL-36γ levels were higher in the allergic rhinitis group, this difference was borderline statistically significant (p= 0.050; Figure 2). Compared with controls, the allergic rhinitis group had significantly higher IgE levels (174 pg/mL; IQR: 58.2 - 480 vs. 40.45 pg/mL; IQR: 20 - 56.85; p <0.001) and eosinophil counts (290 n/mm^3; IQR: 120 - 410 vs. 160 n/mm^3; IQR: 100 - 245); p= 0.010). T-NOSE and VAS scores were also significantly higher in the allergic rhinitis group (p <0.001 for both). Clinical characteristics are summarized in Table 2.

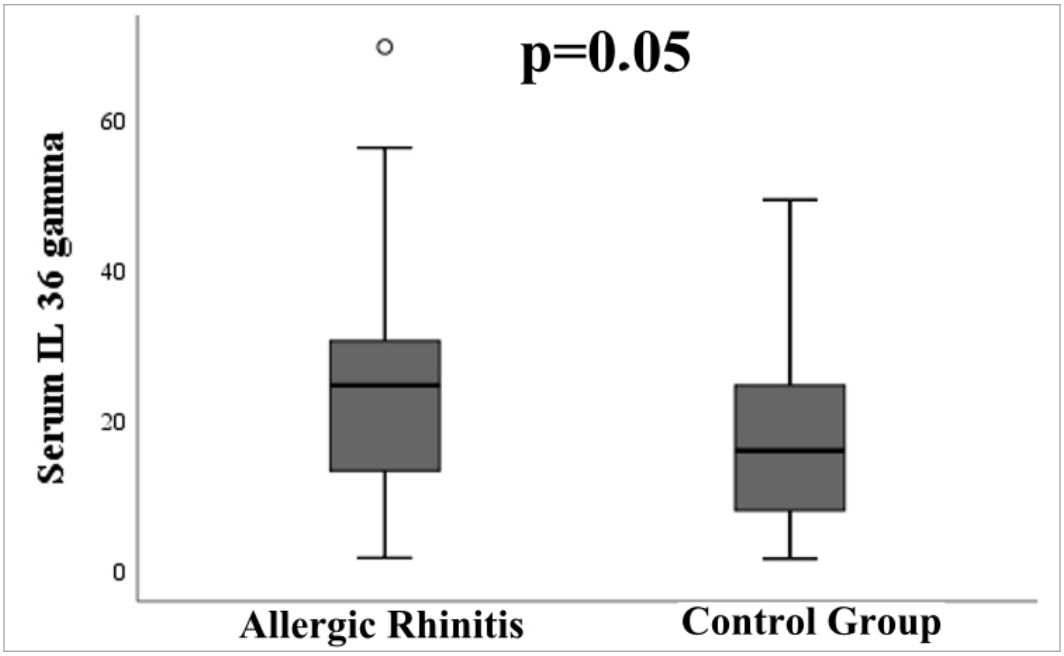

Figure 2. Serum IL-36γ values of allergic rhinitis and control group patients

Table 2. Clinical features

Variables	Allergic Rhinitis (n= 50) Median (IQR)	Control (n= 40) Median (IQR)	*p*
Serum IL-36γ	24.76 (13.42 - 30.67)	16.1 (8.17 - 24.76)	0.050
IgE	174 (58.2 - 480)	40.45 (20 - 56.85)	<0.001
Eozinofil	290 (120 - 410)	160 (100 - 245)	0.010
CRP	0.3 (0.2 - 0.7)	0.65 (0.3 - 1.65)	0.085
T-NOSE score	15 (11 - 18)	2 (1.5 - 3)	<0.001
VAS score	7 (6 - 8)	2 (1 - 2)	<0.001

Mann-Whitney U test.

Table 3. Allergic Rhinitis Patients' Features

Variables	n	%
Disease Severity		
Mild	18	36
Moderate- Severe	32	64
Duration		
Intermittent	18	36
Persistent	32	64
Allergens count		
Single allergen	19	38
Multipl allergens	31	62

Descriptive statistics of disease-related characteristics of allergic rhinitis patients (n= 50) are shown in Table 3.

The relationship between demographic characteristics of patients with allergic rhinitis (n= 50) and serum IL-36γ values is evaluated in Table 4.

Serum IL-36γ values of allergic rhinitis and control group patients in females and males are compared in Table 5. Serum IL-36γ values of female patients with allergic rhinitis were found to be significantly higher than those of female patients in the control group (p= 0.044; Figure 3).

Table 4. Serum IL-36γ values according to the demographic characteristics of the patients (n= 50)

Gender	Serum IL-36γ Median (IQR)	*p*
Male	25.73 (16.31 - 39.55)	0.319
Female	21.3 (9.62 - 30.3)	

Mann-Whitney U test

Table 5. Female vs. Male IL-36γ values between controls and patients

Serum IL-36γ	Male (n= 39) Median (IQR)	Female (n= 51) Median (IQR)
Allergic rhinitis	25.73 (16.31 - 39.55)	21.3 (9.62 - 30.3)
Control	23.32 (10.83 - 33.29)	13.01 (6.28 - 23.06)
p	0.566	0.044

Mann-Whitney U test.

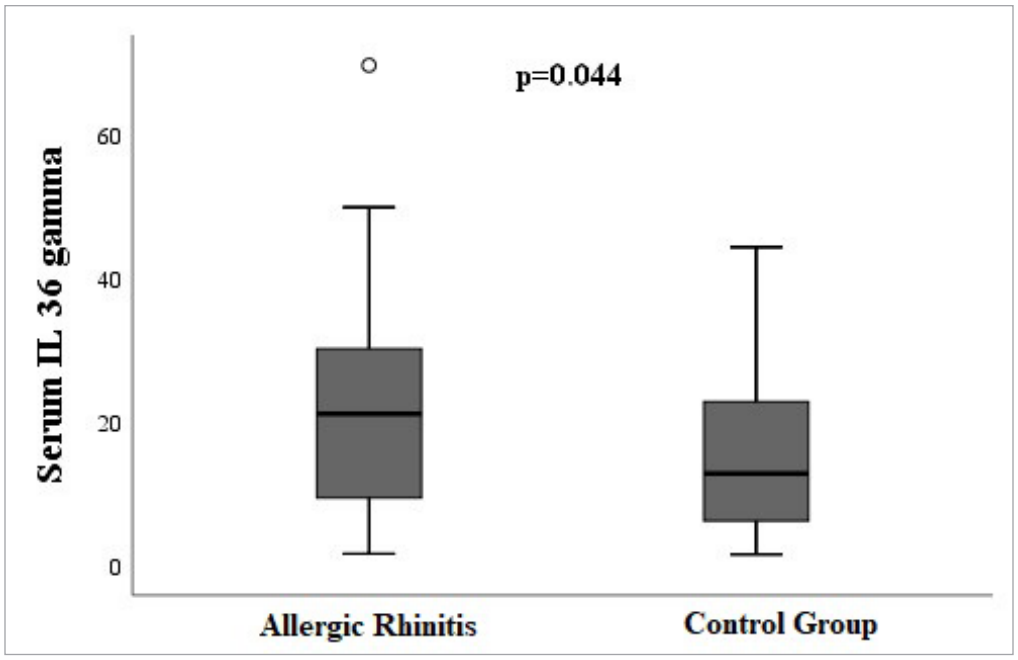

Figure 3. Serum IL-36γ values in female patients compared to the allergic rhinitis and control group

Table 6. Serum IL-36γ values in allergic rhinitis patients according to disease features (n= 50)

Variables	n	Median (IQR)	p
Mild	18	26.24 (13.97 - 28.95)	0.928
Moderate-Severe	32	18.97 (13.01 - 40.54)	
Intermittent	18	28.64 (16.31 - 34.45)	0.067
Persistent	32	18.16 (10.7 - 26.75)	

Mann-Whitney U test.

Table 7. Serum IL-36γ Values due to disease duration vs severity in patients (n= 50)

Duration	Allergic rhinitis severity		*p*
	Mild Median (IQR)	Moderate-Severe Median (IQR)	
Intermittent (n= 18)	26.94 (14.93 - 29.94) (n= 11)	30.67 (16.31 - 50.43) (n= 7)	0.151
Persistent (n= 32)	16.72 (9.62 - 27.07) (n= 7)	18.23 (11.78 - 26.43) (n= 25)	0.929

Mann-Whitney U test.

Table 8. Correlation of Serum IL-36γ and other parameters in allergic rhinitis patients

Variables	Allergic Rhinitis (n= 50)		Male (n= 22)		Female (n= 28)	
	r	p	r	p	r	p
Age	-0.224	0.117	-0.320	0.146	-0.078	0.692
Body mass index	-0.112	0.439	-0.133	0.554	-0.142	0.470
IgE	-0.345	0.014	-0.347	0.113	-0.422	0.025
Eosinophil	-0.202	0.159	-0.015	0.948	-0.412	0.029
C-Reaktif Protein	0.072	0.620	0.252	0.257	-0.017	0.931
T-NOSE scores	-0.050	0.731	0.293	0.186	-0.278	0.152
VAS	-0.015	0.915	0.227	0.310	-0.115	0.559

Spearman correlation test

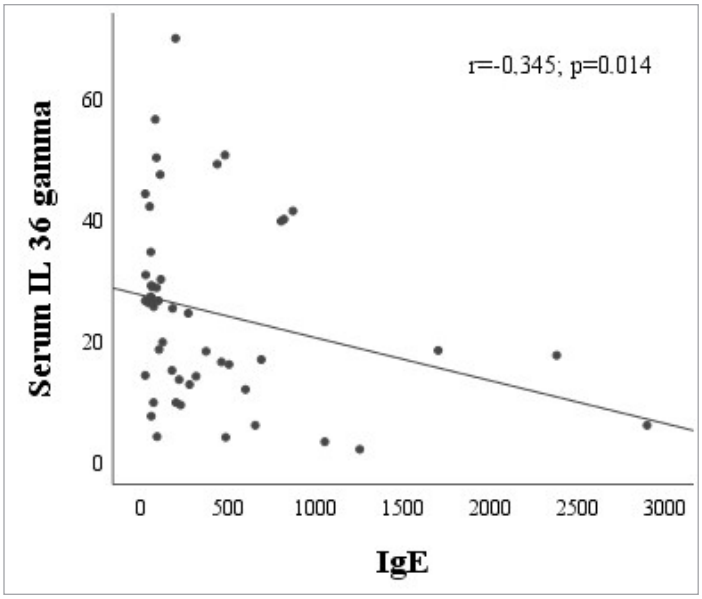

Figure 4. Serum IL-36γ and IgE correlations in allergic rhinitis patients

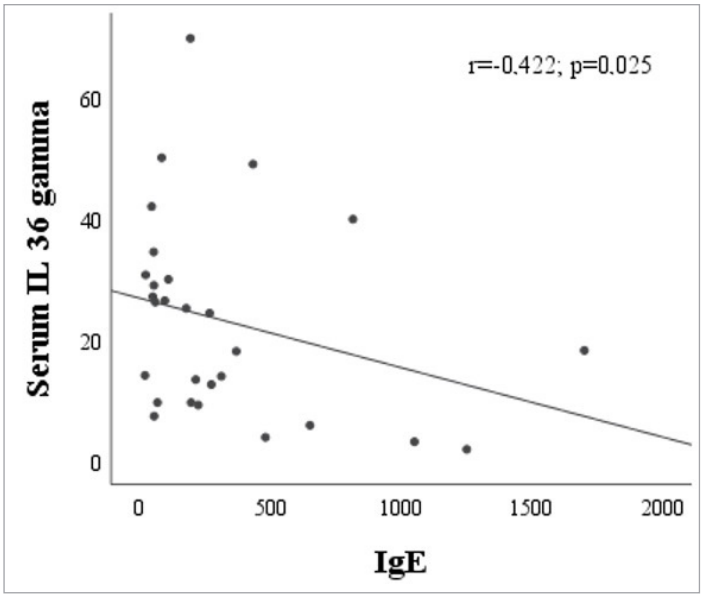

Figure 5. Correlation of Serum IL-36γ and IgE in female patients with allergic rhinitis

Serum IL-36γ levels according to disease characteristics are presented inTable 6. When comparing patients with mild intermittent allergic rhinitis to those with moderate-severe persistent disease, IL-36γ levels were higher in the mild intermittent group. However, this difference was not statistically significant (p= 0.342). Similarly, moderately severe intermittent patients had higher IL-36γ levels than mild persistent patients, but without statistical significance (p= 0.085). Results are presented in Table 7.

Correlation analysis results between serum IL-36γ and other parameters in allergic rhinitis patients (n= 50) are shown inTable 8. A weak but statistically significant negative correlation was observed between serum IL-36γ and IgE levels (r= -0.345; p= 0.014; Figure 4). Weak negative correlations with age and eosinophils were also found but were not statistically significant (p= 0.117 and p= 0.159, respectively).

In male allergic rhinitis patients (n= 22), a weak negative correlation was found between serum IL-36 and age, IgE, and complaint duration, and a weak positive correlation with CRP, T-NOSE, and VAS score; however, the findings were not statistically significant (p >0.05).

In female allergic rhinitis patients (n= 28), there was a moderate negative correlation between serum IL-36γ and IgE (r= -0.422; p= 0.025; Figure 5) and eosinophils (r= -0.412; p= 0.029; Figure 6). Serum IL-36γ values of female patients and T-NOSE score were observed to be weakly negatively correlated, but it was not statistically significant (p= 0.152).

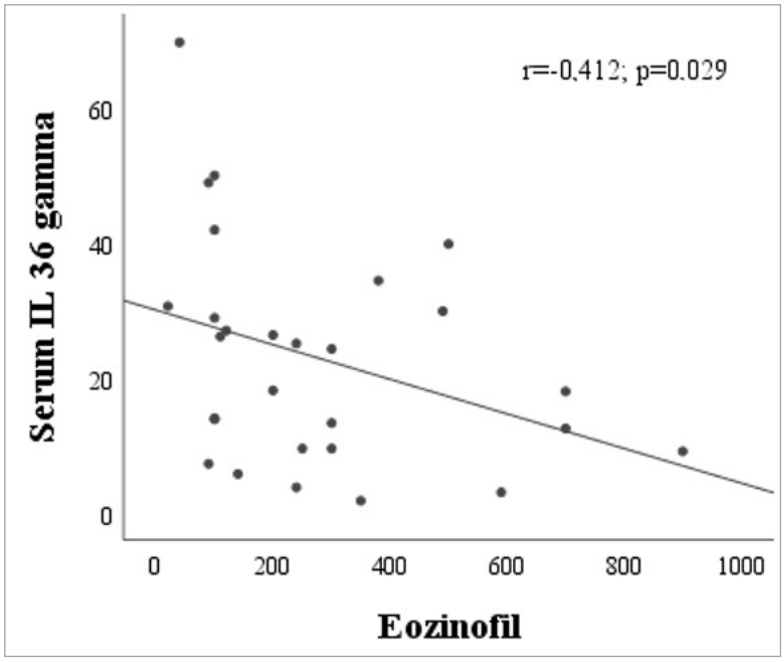

Figure 6. Serum IL-36γ and eosinophil correlation in female patients with allergic rhinitis

Discussion

Allergic rhinitis is a**highly prevalent**(**original: widespread**) global public health problem. Although its prevalence varies across studies, it has been reported to range from**2-25% in children and 1-40% in adults**, affecting approximately**500 million people worldwide**[1].

Allergic rhinitis has a**substantial impact**on quality of life, particularly in childhood, where it can impair school performance, contribute to sleep disorders, and cause social and physical dysfunction. It also imposes a**considerable burden** on healthcare systems [11]. Since the etiopathogenesis of allergic rhinitis is not yet fully understood, further investigation into its underlying mechanisms remains important.

Multiple risk factors have been implicated in the development of allergic rhinitis, including family history of atopy, male sex, obesity, and passive smoking[12]. In our study, we evaluated sex distribution, family history of atopy, exposure to passive smoking, body mass index, and serum total IgE levels in children with allergic rhinitis. The family history of atopy was significantly higher among allergic rhinitis patients (60%) compared to controls (20%) (p <0.001). Passive smoking exposure was also significantly more frequent in the Allergic rhinitis group (50% vs. 27.5%, p= 0.030). Body mass index did not differ significantly between groups.

Epidemiological studies have shown varying results regarding sex differences in allergic rhinitis prevalence. Some report higher rates in males during childhood [13], while others suggest that allergic rhinitis prevalence may be higher in females after puberty due to hormonal influences [14]. In our study, although allergic rhinitis was more common in females, the difference was not statistically significant. The mean age of diagnosis in our cohort (**11.58 ±3.81 years**) was consistent with previous reports (mean 9.05 ±1.93 years) [,12].

Elevated serum total IgE levels, while not specific to allergic rhinitis, are considered a marker of allergen sensitization and a risk factor for the disease [12]. Cardinale *et al.* [15], reported significantly higher serum total IgE levels in children with allergic rhinitis compared to controls. Our findings were consistent with these results (***p* <0.001**), reinforcing the

association between high serum IgE levels and allergic rhinitis. However, serum total IgE alone may not be sufficient for diagnosis due to possible false-negative results; therefore, allergen-specific IgE testing is often necessary [16,17]. In our study, all allergic rhinitis patients had positive skin prick test results and at least one positive serum respiratory allergen-specific IgE.

The pathophysiology of allergic rhinitis involves early- and late-phase allergic responses. In the early phase, mast cell degranulation releases mediators responsible for sneezing, itching, rhinorrhea, and nasal congestion. The late phase, occurring 2-4 hours later, is characterized by infiltration of eosinophils, basophils, neutrophils, macrophages, and T lymphocytes, leading to persistent nasal obstruction. Eosinophils, in particular, play a central role by releasing cytotoxic proteins and cytokines that perpetuate inflammation. Major basic protein, eosinophilic cationic protein, and leukotrienes previously synthesized in eosinophils are secreted from degranulating eosinophils, causing epithelial damage. Th2 cells also release IL-3, 4, 5 and other cytokines during this reaction, resulting in more eosinophil chemoattraction to the tissue. Cell infiltration and secreted mediators in this tissue cause nasal congestion, the main symptom of the late phase, and the main responsible cells are eosinophils. In this way, eosinophils, which are known to play a cellular role in IgE and allergen immune response, were evaluated in childhood allergic rhinitis studies [18]. Eosinophil levels were found to be significantly higher in serum. We obtained similar results in this study and found serum eosinophil (290; IQR: 120-410 and 160; IQR: 100-245; p= 0.010) values to be higher than those of the control group.

Tests such as T-NOSE (Total nasal obstruction evaluation) Score and VAS (Visual analogue scale) can be used subjectively to quantitatively measure the severity of the disease in the clinic to provide disease-specific criteria in allergic rhinitis [19,20]. Filiz *et al.*[21], evaluated the T-NOSE and VAS scores of pediatric allergic rhinitis patients in their study, and the values, which were found to be significantly high, also increased in correlation with the severity of the disease. In our study, T-NOSE and VAS scores were observed to be higher in the patient group (p <0.001).

There are unexplained processes in the allergic inflammation pathway. Among these, Interleukin 36 (formerly known as IL1F9), a member of the IL-1 cytokine family, whose place at the level of cytokines and mediators has been discussed in recent studies, has been identified and continues to be investigated at the cellular level. As is known, IL-36 comprises three sub-members: alpha, beta, and gamma. Among these, IL-36γ is most implicated in allergic rhinitis, contributing to its etiology by prolonging eosinophil life span, enhancing adhesion, and promoting activation. To date, there is no pediatric allergic rhinitis patient group study on IL-36γ, so this study is a first in terms of pediatric allergic rhinitis research. In a study conducted in adult age groups reported in the literature [8,9]. They stated that serum IL-36γ levels and mRNA expressions were found to be significantly higher in allergic rhinitis patients than in the control group. In this study, we calculated the median serum IL-36γ value of patients with allergic rhinitis as 24.76 pg/mL (IQR: 13.42 - 30.67) and the control group as 16.1 pg/mL (IQR: 8.17 - 24.76). Serum IL-36γ values of patients with allergic rhinitis were higher than those of the control group and were found to be borderline statistically significant (p= 0.050).

Studies on IL-36 family cytokines in the etiopathogenesis of allergic rhinitis are quite rare. The basic members of this family have been shown so far as alpha, beta and gamma. In the study conducted by Qin *et al.*[8], although alpha, beta and gamma serum levels were all high in adult patients with allergic rhinitis, IL-36γ levels were found to be the highest. IL-36γ regulates the survival, migration and activation of eosinophils during allergic rhinitis through p38 gene-mediated MAPK/MEK pathways. This proves that it is an essential pathway to control inflammation in allergic rhinitis by regulating eosinophils, which are the primary effector cells. Similar to the study conducted by Qin *et al.* [9], in adult allergic rhinitis patients, we found serum IL-36γ values to be higher compared to the control group in our study, which was conducted in the pediatric population for the first time in the literature. These results were borderline statistically significant (p= 0.050). A significance level as dominant as that in adult patients was not detected in the pediatric population. It was thought that studies to be conducted in larger patient groups in the pediatric population could produce results with a higher degree of significance.

No study could be identified in the literature that evaluated the relationship between allergic rhinitis disease severity or frequency, duration, and IL-36γ in the adult or pediatric population. In the patient group with allergic rhinitis (n= 50), when the mild and moderate-severe groups were compared according to disease severity, the relationship between serum IL-36γ was found to be higher in the mild group. Still, it was not found to be statistically significant (p= 0.928). In addition, when the frequency of allergic rhinitis is examined, the median serum IL-36γ value of persistent allergic rhinitis patients is 18.16 pg/mL (IQR: 10.7-26.75), and that of intermittent patients is 28.64 pg/mL (IQR: 16.31- 34.45). This difference was not statistically significant (p= 0.067). Thus, IL-36γ serum levels did not differ significantly with disease severity and duration of incidence. In addition, no statistically significant difference was detected when the complaint durations were grouped as less than or more than 2 years, thus showing that there was no relationship between the duration of exposure to the disease and IL-36γ values.

In the mild intermittent, mild persistent, moderate-severe intermittent, and moderate-severe persistent disease groups, where the frequency and severity groups were evaluated together, the highest median IL-36γ value was detected in the moderate-severe intermittent group, 30.67 pg/mL (16.31 - 50.43), but no statistically significant difference was shown (p= 0.151).

In the study conducted by Qin *et al.* [8], it was shown that IL-36γ levels act together with changes in eosinophilic activation and functions, and there is an increase in correlation with eosinophil levels in allergic rhinitis patients. In our study, a weak negative correlation was observed between serum IL-36γ and eosinophil levels, but it was not statistically significant (r= -0.202, p= 0.159). These results can be interpreted as a negative difference in the IL-36γ effect on eosinophils in the pediatric population compared to adults.

Interestingly, IL-36γ levels were negatively correlated with serum IgE in our study (**r= -0.345, p= 0.014**), a relationship not previously reported. This may indicate a potential suppressive interaction at higher IgE levels, although further research is required to clarify the mechanism. In female patients, IL-36γ levels were significantly higher than in female controls (**p= 0.044**) and showed moderate negative correlations with both IgE and eosinophils. This suggests a possible sex-related difference in IL-36γ regulation, potentially influenced by hormonal factors [22-24]. New and extensive studies on the IL-36γ and IgE relationship are needed.

Due to the nature of allergic rhinitis in children, there may be differences in the biomolecules used for diagnosis. In this study, when male and female patients were compared with each other, serum IL-36γ values were determined to be higher in males, but this difference was not significant (p= 0.319). Apart from this, when the IL-36γ values of the control group and gender were compared separately, it was determined that the serum IL-36γ values of female patients with allergic rhinitis were statistically significantly higher than those of female patients in the control group (p= 0.044). At the same time, there was no significant difference in male patients. Additionally, in female allergic rhinitis patients (n= 28), a moderate negative correlation was determined between serum IL-36γ and IgE (r= -0.422; p= 0.025) and eosinophils (r= -0.412; p= 0.029). This was similar to the negative correlation between IgE and eosinophils in the general part of our study. No correlation was found with these values in male patients. Significantly higher levels of IL-36γ in females compared to the control group suggest that it can be used as a gender-related marker for allergic rhinitis. Gender-related hormonal changes may explain the lack of a significant change in males. Different results may be obtained in studies larger than the population in which this study was conducted.

Our study is the first to evaluate IL-36γ in pediatric allergic rhinitis and its associations with disease characteristics. However, the relatively small sample size and lack of multivariate analysis are limitations. Larger studies are needed to confirm our findings and elucidate the molecular mechanisms linking IL-36γ to pediatric allergic rhinitis.

Conclusion

In this first pediatric study assessing serum IL-36γ in allergic rhinitis, we found higher levels in AR patients compared with controls, with borderline statistical significance. Female patients exhibited significantly higher IL-36γ levels than female controls, suggesting a potential role as a sex-specific biomarker. Serum IL-36γ was inversely correlated with total IgE levels, particularly in females.

Future prospective studies with larger sample sizes should investigate IL-36γ in pediatric allergic rhinitis, considering sex-related differences, to determine its clinical utility in assessing disease severity and guiding management.

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