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ORIGINAL ARTICLE

Blood eosinophil counts as a biomarker for allergen sensitization in childhood allergic diseases in comparison with total IgE

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Purpose: Eosinophils and total immunoglobulin (IgE) have served as a histologic hallmark of allergic conditions. Many investigators have used total eosinophil count (TEC) and total IgE for evaluating allergic diseases. We examined differences in TEC and total IgE in allergic diseases and whether it differs according to sensitization.

Methods: In this retrospective study, we enrolled 551 patients who visited Uijeongbu St. Mary's Hospital from January 1, 2009 through December 31, 2012 for allergic diseases. We included patients with a diagnosis of atopic dermatitis (AD), allergic rhinitis (AR), asthma (AS), or urticaria (UC). We compared the TEC and total IgE level according to sensitization patterns.

Results: There were 235 cases of AD, 179 cases of AS, 112 cases of AR, and 82 cases of UC. Regarding sensitization, 106 were not sensitized to any allergens, 206 were sensitized to inhalants, 109 were sensitized to food allergens, and 49 were sensitized to both food and inhalant allergens. TEC was significantly higher in the AD and AR group than in the UC group. TEC was significantly higher in those sensitized to both inhalant and food than those not sensitized. The total IgE levels were significantly higher in those sensitized to both inhalant and food than those not sensitized or sensitized to food. Total IgE levels were significantly higher in those sensitized to inhalant than those not sensitized or sensitized to food.

Conclusion: Eosinophils appear to play differential roles in the expression of different types of allergic diseases. Total IgE level may play a significant role in sensitization. (*Allergy Asthma Respir Dis 2024;12:26-30*)

Keywords: Eosinophils, Immunoglobulin E, Allergen, Hypersensitivity

INTRODUCTION

Recent approaches to patients with allergic diseases include the application of single or multiple biomarkers such as eosinophils and IgE in disease phenotype and endotype analysis to determine disease prognosis and identify patients eligible for treatment.[1,2] Eosinophils have served as a histologic hallmark of many diseases, especially infections and systemic and allergic conditions. In other circumstances, eosinophils may also serve as surrogate markers of disease activity as in asthma (AS), atopic dermatitis (AD), allergic rhinitis (AR), and allergic conjunctivitis (AC).[3] Eosinophil predominance characterizes many diseases, but the true impact of these cells on the human condition is not certain. Some studies have suggested that peripheral blood eosinophil levels or peripheral levels of unique eosinophil-specific markers correlate with allergic disease severity, such as AS, AR, and AD.[4-6]

Many investigators have used total eosinophil count (TEC) and total serum immunoglobulin E (IgE) for evaluating allergic disease.[7,8] Sixty to 90% of AS and 20 to 70% of AD have been proven to be IgE mediated.[9] Previous studies have attempted to predict disease activity and treatment response in allergic diseases through TEC, total or specific IgE.[10,11] However, it is still not clear whether these biomarkers show distinct differences or correlations depending on pediatric allergic diseases. In this study we examined the differences in TEC in allergic diseases and whether it differed according to sensitization. We also investigated if there was any association between TEC and total IgE.

MATERIALS AND METHODS

We reviewed the medical records of 551 patients who visited the Uijeongbu St. Mary's Hospital, allergy clinic of the pediatric de-

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partment from January 1, 2009 to December 31, 2012 for allergic diseases. We included patients who had documentation of clinical criteria sufficient for the diagnosis of AD, AR, AS, or urticaria (UC). This study was approved by the Institutional Review Board at The Catholic University of Korea (IRB No. XC20WIDI0144).

1. Clinical diagnostic criteria

AR was diagnosed based on individual symptoms and nasal examination findings that fulfilled the criteria for AR, including mucosal edema, pale/bluish discoloration, and watery discharge.[12] AD diagnosis was based on the age-appropriate clinical criteria for allergic eczema in childhood.[13] For AS, the diagnosis was based on recurrent wheezing or cough without a cold in the preceding 12 months with evidence of bronchial hyperresponsiveness upon methacholine challenge (PC_{20} [provocative concentration of methacholine causing a 20% fall in forced expiratory volume in 1 second] ≤ 8 mg/mL) or at least 12% reversibility of forced expiratory volume in 1 second after inhalation of a short-acting bronchodilator.[14] With younger children (under 5 years of age) or when such evidence was not readily available: the diagnosis was based on a history of 3 or more episodes of at least 2 of the following – persistent daytime or nighttime cough, physician-diagnosed non-febrile wheezing, recurrent episodes of shortness of breath or exercise-induced shortness of breath and cough. UC was limited to acute cases lasting for less than 6 weeks and was defined as a disease characterized by the development of wheals (hives), angioedema, or both.[15] These data were obtained from the patient's clinical records, clinic interviews, and medical examination results.

2. Peripheral blood analysis

The number of peripheral blood eosinophils was counted with blood samples containing ethylenediaminetetraacetic acid using an automated hematology analyzer (XE2100 D; Sysmex Co., Kobe, Japan). Serum total IgE level was measured using ImmunoCAP (Thermofisher AB, Uppsala, Sweden) according to the manufacturer's instructions.

3. Measurement of specific IgE

Specific IgE levels were measured using the ImmunoCAP (Thermofisher AB). A specific IgE test was performed with 6 allergens common in Korea: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, egg whites, cow milk, German cockroach, and *Alternaria alternata*. Sensitization was defined as 0.35 KU/L or higher specific IgE to one or more allergens.

4. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). All continuous variables are expressed as mean ± standard deviation, and numbers (n) with percentages are expressed for categorical variables. Normally distributed variables were analyzed with analysis of variance and for those that were not normally distributed, the Kruskal-Wallis and Mann-Whitney *U* 2-tailed tests were used for analysis. The chi-square test was used to examine differences between categorical variables between groups. Statistical significance was defined at $P < 0.05$ in a 2-tailed test.

RESULTS

1. Subject Characteristics

The subject characteristics of the study are shown in Table 1. The study population included 551 patients and the median age was 4 years (interquartile range, 1.0–8.0 years). Three hundred twenty-seven (59.3%) were male. There were 235 cases of AD, 179 cases of AS, 112 cases of AR, and 82 cases of UC. In the study group, 548 (99.5%) completed TEC, 463 (84.0%) completed total IgE, and 471 (85.5%) completed specific IgE by ImmunoCAP test. Regarding sensitization, 106 were nonsensitized, 206 were sensitized to inhalant allergens, 109 were sensitized to food allergens, and 49

Table 1. Subject characteristics (N = 551)

Characteristic	Value
Male sex	327 (59.3)
Age (yr), median (IQR)	4 (1.0–8.0)
Allergic disease	
Atopic dermatitis	235 (42.6)
Asthma	179 (32.5)
Allergic rhinitis	112 (20.3)
Urticaria	82 (14.9)
Sensitization	
None	106 (22.5)
Inhalant	206 (43.7)
Food	109 (23.1)
Inhalant and food	49 (10.4)
Total eosinophil count (cells/μL)	427.4 ± 386.8
Total IgE (IU/mL)	364.3 ± 659.3

Values are presented as number (%) or mean ± standard deviation unless otherwise indicated.
IQR, interquartile range; IgE, immunoglobulin E; IU, international unit.

were sensitized to both food and inhalant allergens.

2. Eosinophil

TEC was significantly higher in the AD and AR groups compared with the UC group (Fig. 1). According to the sensitization pattern, TEC was significantly higher in those sensitized to both inhalant and food allergens than those nonsensitized (Fig. 2).

3. Total IgE

The level of total IgE according to allergic diseases was not significantly different (Table 2). According to the sensitization pattern, the level of total IgE was significantly higher in those sensitized to both inhalant and food allergens than nonsensitized group and food-sensitized group. The level of total IgE was also significantly higher in those sensitized to inhalant allergens than nonsensitized and those sensitized to food allergens (Fig. 3).

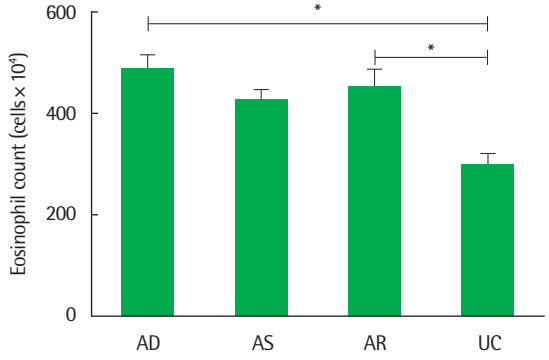

Fig. 1. Total eosinophil count in allergic disease. AD, atopic dermatitis; AS, asthma; AR, allergic rhinitis; UC, urticaria. *P<0.05.

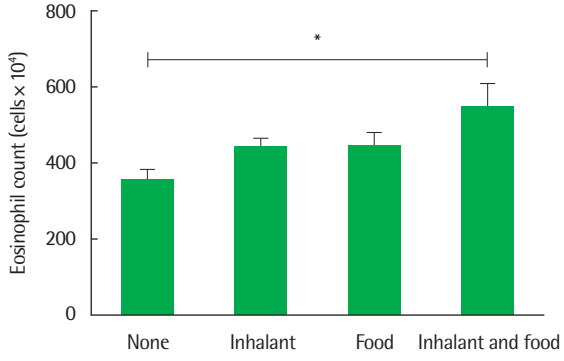

Fig. 2. Eosinophil count according to pattern of sensitization. *P<0.05.

DISCUSSION

This study investigated the difference of TEC in allergic diseases and sensitization and compared it with total IgE. TEC was significantly higher in AD and AR than UC, but there was no significant difference in the level of total IgE according to allergic diseases. Regarding pattern of sensitization, TEC was significantly higher in those sensitized to both food and inhalant allergens than those nonsensitized. The level of total IgE was significantly higher in those sensitized to both inhalant and food allergens than the nonsensitized group and food-sensitized group. The level of total IgE was also significantly higher in those sensitized to inhalant allergens than nonsensitized and those sensitized to food allergens.

Eosinophils are involved in host defense, immune and adaptive responses, tissue damage, and airway remodeling.[16] Eosinophils play an important role in defense against infections and are a key element in allergic diseases. It is strongly associated with disorders involving mucosal surfaces, particularly AS and AR, which exhibit a significant correlation with the number as well as activation status of tissue infiltrating eosinophils.[17] Eosinophils may also serve as surrogate markers of disease activity in AS, AD, AR, and AC.[3] There is some evidence that allergic multimorbidity and severity

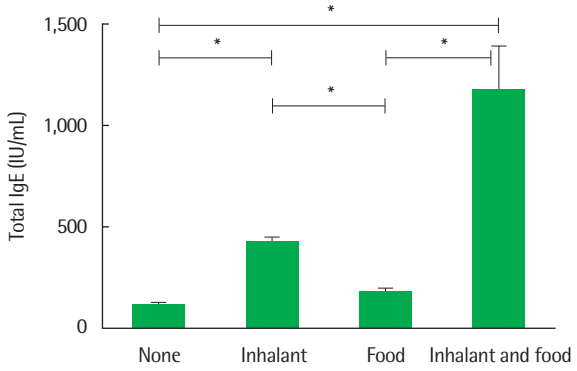

Fig. 3. Level of total IgE according to sensitization pattern. IgE, immunoglobulin E. *P<0.05.

Table 2. Total IgE according to allergic disease

	AD (n=179)	AS (n=162)	AR (n=105)	UC (n=73)	*P*-value
Total IgE (IU/mL)	387.3±842.7	422.4±512.9	447.3±632.8	183.3±661.3	0.041*

IgE, immunoglobulin E; AD, atopic dermatitis; AS, asthma; AR, allergic rhinitis; UC, urticaria.
*There was no statistically significant difference after Bonferroni test.

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are associated with increased markers of type 2 inflammation, such as blood eosinophils and markers of eosinophil activation, such as eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN).[18] Serum ECP and EDN levels were significantly higher in atopic AS than in nontopic AS or control group, and higher in moderate to severe group than in mild AS. Eosinophil predominance characterizes such allergic diseases, but the true impact of these cells in human conditions is not certain. Previous studies have found that the presence of inflammatory cells including eosinophils in the airways did not diagnose AS, but their measurement was especially useful for the clinical assessment of bronchitis, guiding treatment with corticosteroids and long-term therapy of AS.[19] Another study reported that blood eosinophil counts and derived ratios could accurately predict eosinophilic AS in patients with persistent uncontrolled AS despite treatment.[20]

Eosinophils have been suggested to be implicated in urticarial disease.[21] In our study, we found that TEC was significantly higher in AD and AR in comparison with UC, but such differences were not observed with AS. The potential role of eosinophils in the inflammatory process of UC is supported by their association with urticarial skin lesions in individuals with eosinophilic disorders such as hypereosinophilic syndrome.[22] Some previous studies have described a definite rise in eosinophil counts during the acute phase of UC.[23] In contrast, eosinopenia has been reported to be associated with higher disease activity in chronic spontaneous UC patients.[24] These conflicting results demonstrate the complex role of eosinophils in urticarial disease. There are few reports, and little is known about the impact of eosinophilic UC on the ongoing disease course, especially in children. Further study will be needed to understand the differential role of eosinophils in the expression of allergic diseases.

Previous animal studies have suggested that eosinophils were unlikely to participate in allergen sensitization, including antigen priming of T cells[25] or the development of significant humoral responses.[26] Other studies showed that in allergen provocation models, the loss of eosinophils specifically during the respective allergen sensitization phases had no effects on the subsequent development of Th2 immune responses and inflammatory metrics (including the development of robust airway eosinophilia) following allergen challenge.[27] This was different from our study in which we found that TEC was significantly higher in those sensitized to both food and inhalant allergens than those nonsensitized. Further study to determine the role of eosinophils in sensitization in humans and whether it differs from animal models seems worthy.

The level of total IgE in human serum depends on several factors, such as genetic predisposition, sex, race, environmental factors, and type of disease (allergy, parasitic infection, or immune deficiency).[28] Association with total IgE and allergic disease has been discrepant: previous studies suggested that a high concentration of IgE was correlated with AD and AS.[29,30] However, a different study reported no significant association with total IgE and allergic disease based on questionnaires.[31] Likewise, we found no significant difference in the level of total IgE according to allergic disease.

Only a few studies have examined the relationship between total IgE concentrations and the development of sensitization to different types of allergens. One of the studies reported that allergen-specific IgE sensitization occurs in relation to total IgE concentration.[32] This was supported by our study, in which we found that the level of total IgE was significantly higher in those sensitized to both inhalant and food allergens than nonsensitized group and food-sensitized group. In addition, we found that the level of total IgE was different according to the pattern of sensitization. Further study will be needed to elucidate the role of total IgE in the pattern of sensitization.

One limitation of the study was that the subjects were selected from a tertiary hospital located in the northern part of South Korea. Therefore, our data may not represent the characteristics of the Korean population. Secondly, although the subjects were limited to less than 18 years of age, the age at enrollment varied largely. Lastly, this retrospective study was based on only limited data, including sensitization analysis of 2 inhalant allergens: cockroach and Alternaria, excluding house dust mites. More extensive studies are needed, including analysis of various groups of inhalant allergens, along with biomarkers, age and severity of allergic disease.

In conclusion, eosinophils appear to play a differential role in the expression of different types of allergic diseases. The level of total IgE seems to play a significant role in sensitization. Further study will be needed to elucidate the role of eosinophils and total IgE in allergic diseases.

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