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Original Article

Correlation of immunoglobulin E, eosinophil cationic protein, and eosinophil count with the severity of childhood perennial allergic rhinitis

Shuei-Tu Chen[1], Hai-Lun Sun[1,2], Ko-Hsiu Lu[2], Ko-Huang Lue[1,2], Ming-Chih Chou[2]

[1]Division of Allergy, Asthma and Rheumatology, Department of Pediatrics, Chung Shan Medical University Hospital, Taichung; and [2]Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan

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Background and Purpose: Elevated levels of serum total immunoglobulin E (IgE), serum allergen-specific IgE, serum eosinophil cationic protein (ECP), blood eosinophil count and nasal eosinophil count are considered to be associated with allergic rhinitis (AR), but the relationships between these allergic inflammatory markers and the clinical severity of AR remain controversial. This study aimed to clarify these relationships.
Methods: 186 children aged 2 to 12 years old were selected, including 160 with perennial AR (PAR) and 26 with non-AR as controls. The total nasal symptom score was calculated for each patient from a questionnaire and correlated with data on serum total IgE, serum allergen-specific IgE, serum ECP, and eosinophil count in blood and nasal smear.
Results: Levels of all allergic inflammatory markers in children with PAR were significantly different from those in non-allergic children, except for serum ECP. All of the markers were related to the severity of PAR in bivariate correlation analysis. On multiple linear regression analysis, however, only nasal eosinophil count (p<0.001) and serum allergen-specific IgE (p=0.005) were independent predictors.
Conclusion: These results suggest that nasal eosinophil count, an organ-specific allergic inflammatory marker, and serum allergen-specific IgE, a systemic allergic inflammatory marker, are correlated with the severity of PAR in children.

Key words: Eosinophil cationic protein, eosinophils, immunoglobulin E, perennial allergic rhinitis

Introduction

Allergic rhinitis (AR) is among the most common allergic diseases and affects 25-35% of the world population [1]. The prevalence of AR in children is higher than that for the general population, with previously reported rates of up to 42% in the United States [2], and it is still increasing.

AR is induced by an immunoglobulin E (IgE)-mediated inflammatory reaction following allergen exposure of the mucous membranes lining the nose, and is associated with eosinophilic infiltration. The clinical symptoms are characterized by nasal itching, sneezing, rhinorrhea and nasal congestion. The diagnosis is confirmed by a clinical history of typical allergic symptoms and in vivo or in vitro tests for detection of free or cell-bound IgE [1]. Thus, levels of IgE, eosinophils and eosinophil cationic protein (ECP; a mediator released from activated eosinophils) are usually considered to be correlated with AR.

Several studies have suggested that elevated serum total IgE [3-5], serum allergen-specific IgE [4,6,7], serum ECP [3,4,8,9], blood eosinophil count [4,5,7, 10,11], or nasal eosinophil count [5,12-18] are associated with AR. On the other hand, other studies have found no association between serum total IgE [6,19], serum allergen-specific IgE [20,21], blood eosinophil count [9,14,22], or nasal eosinophil count and AR [22,23]. Indeed, the relationship between these allergic inflammatory markers and the clinical severity of AR remains controversial. This study investigated the correlations between these markers and the severity of AR.

Corresponding author: Ko-Huang Lue M.D., Division of Allergy, Asthma and Rheumatology, Department of Pediatrics, Chung Shan Medical University Hospital, No. 110, Sec. 1, Chien-Kuo N. Road, Taichung 402, Taiwan.
E-mail: cshy095@csh.org.tw

Methods

Patients

The study recruited 186 patients aged 2 to 12 years, including 160 children with perennial AR (PAR) and 26 children with persistent non-AR as controls. The inclusion criteria were as follows: 1) a documented clinical history of persistent rhinitis for at least 1 year; and 2) a positive response to mite-specific IgE (CAP system; Pharmacia, Uppsala, Sweden) to confirm allergy. Exclusion criteria were as follows: 1) use of corticosteroids or sodium cromoglycate within the past 4 weeks; 2) use of histamine H1 antagonist and/or decongestant within the past 7 days; and 3) presence of nasal abnormalities, concurrent purulent nasal infection, past history of asthma, or any other significant medical conditions. Written informed consent for participation was obtained from the guardians of all patients. The study was approval by the Chung Shan Medical University Hospital Institutional Review Board.

Study design

Patients were divided into 2 groups: 1) 160 children with PAR; 2) 26 controls with non-AR. The PAR group was further divided into those younger than 6 years old and those aged between 6 and 12 years. At the screening visit, medical history was taken, and physical examination and serum allergen-specific IgE test were conducted. At the second visit, the serum total IgE level, serum ECP level, and peripheral blood eosinophil count were evaluated, and nasal scrapings were collected. Guardians were requested to complete the nasal symptoms questionnaire.

Nasal symptoms questionnaire

Guardians were instructed to complete the symptoms questionnaire items, including nasal itching, sneezing, rhinorrhea and nasal congestion using a seven-point scale as follows: (0) none; not noticeable; (1) none-to-mild, between none and mild; (2) mild, noticeable but not bothersome; (3) mild-to-moderate, between mild and moderate; (4) moderate, noticeable and bothersome some of the time; (5) moderate-to-severe, between moderate and severe; (6) severe, bothersome most of the time and/or very bothersome.

Serum total IgE and serum ECP

Peripheral blood was collected and the separated serum was kept at –20°C. Serum total IgE (IU/mL) and ECP (ng/L) were then determined by enzyme-linked immunosorbent assay method (CAP system). The detectable range of the assay for total IgE is 2 to 2000 IU/mL, and for serum ECP is 2 to 100 ng/L.

Allergen-specific IgE

Specific IgE against *Blomia tropicalis*, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blatella germanica*, cat dander, dog dander, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Candida albicans*, and *Penicillium notatum* were measured using the CAP system. The detectable range of specific IgE for this assay is 0.35 to 100.00 IU/mL, and the titers are classified as valence 0-6 according to the results: valence 0 (0-0.35 IU/mL), valence 1 (0.36-0.70 IU/mL), valence 2 (0.71-3.50 IU/mL), valence 3 (3.51-17.50 IU/mL), valence 4 (17.51-50.00 IU/mL), valence 5 (50.01-100.00 IU/mL), valence 6 (>100.00 IU/mL). In order to evaluate the relative contribution of the varieties of allergens and the valence of positively reactive allergens to correlation with AR severity, 3 additional evaluations were conducted as follows: CAP1 evaluated the number of positively reactive allergen-specific IgE among the 10 allergens (positive number of allergen-specific IgE); CAP2 determined the maximum valence of allergen-specific IgE among the 10 allergens; and CAP3 evaluated the sum of valence of allergen-specific IgE of the 10 allergens.

Blood eosinophil count

A peripheral venous blood sample was collected and eosinophils were counted in a Fuchs Rosenthal chamber after staining with eosinophil staining solution. The detectable range of blood eosinophil count using this method is 0 to 10,000/μL.

Nasal smears

After excess secretions were cleared, the middle third of the patient's inferior turbinate was gently scraped with a slender cotton swab, and the collected secretions and cells were smeared onto a glass slide. The slides were then stained with Liu's stain and examined under a light microscope. An experienced cytologist, who was blinded to the clinical status of the patients involved, performed this assay. Eosinophils were viewed at high power (oil immersion, × 1000). Two modes of evaluation were conducted: grading mode (nasal eosinophil grade;SME1) and percentage mode (nasal eosinophil percentage; SME2). In the grading mode, grades were evaluated according to the mean number of eosinophils per 10 high-power fields as follows: (0) 0 cell, (0.5+) 0.1-1.0 cells, (1+) 1.1-5.0 cells, (2+)

Table 1. Characteristics of patients with perennial allergic rhinitis (PAR) and children with non-allergic rhinitis

Variable (n or mean ± SD)	Children with PAR			Children with non-allergic rhinitis (controls) (2-12 years)	*p* (between PAR <6 years and PAR 6-12 years)	*p* (between PAR and control group)
	2-12 years	<6 years	6-12 years			
Number	160	84	76	26		
Male/female	89/71	47/37	42/34	14/12		
Age (years)	6.62 ± 2.66	4.40 ± 1.00	9.08 ± 1.49	5.74 ± 2.48		
Serum IgE (IU/mL)	565.04 ± 541.85	528.70 ± 575.60	605.21 ± 502.65	100.56 ± 142.20	0.606	<0.001[a]
Specific IgE						
Number of allergens (CAP1)	3.35 ± 1.31	3.25 ± 1.41	3.46 ± +1.19	0 ± 0	0.521	<0.001[a]
Maximum valence (CAP2)	4.30 ± 1.41	4.25 ± 1.46	4.36 ± 1.36	0 ± 0	0.869	<0.001[a]
Sum of all valence (CAP3)	11.43 ± 5.01	10.92 ± 5.15	12.00 ± +4.83	0 ± 0	0.304	<0.001[a]
Serum ECP (ng/L)	24.87 + 23.40	21.39 + 18.03	28.73 + 27.80	18.58 + 16.76	0.096	0.423
EOS [/μL]	497.30 ± 101.02	497.50 ± 338.00	497.08 ± 256.25	269.00 ± 199.64	1.000	0.001[a]
Nasal eosinophils						
Grade (SME1)	2.15 ± 1.03	2.05 ± 1.15	2.27 ± 0.88	0.65 ± 0.91	0.349	<0.001[a]
Percentage (SME2) [%]	50.55 ± 33.76	47.08 ± 35.23	54.38 ± 31.85	14.58 ± 26.66	0.338	<0.001[a]
Total nasal symptom score	12.34 ± 4.81	11.76 ± 5.24	12.97 ± 4.24	8.50 ± 4.45	0.240	<0.001[a]

Abbreviations: SD = standard deviation; IgE = immunoglobulin E; CAP1 = positive number of allergen-specific IgE; CAP2 = maximum valence of allergen-specific IgE; CAP3 = sum of valence of allergen-specific IgE; ECP = eosinophil cationic protein; EOS = blood eosinophil count; SME1 = nasal eosinophil grade; SME2 = nasal eosinophil percentage
[a]$p<0.05$.

5.1-15.0 cells, (3+) 15.1-20.0 cells, (4+) >20.0 cells [24]. In the percentage mode, the eosinophil count was expressed as a percentage of the total number of leukocytes.

Statistical analysis

A standard PC with Statistical Package for the Social Sciences (SSPS) for Windows (Version 11.0; SPSS, Chicago, IL, USA) software was used for the statistical analysis. All collected data were expressed as mean ± standard deviation. One-way analysis of variance and Tukey method were used to compare the main data between groups. Bivariate correlation analysis, simple linear regression analysis and multiple linear regression analysis were used to compare the correlations among markers and total nasal symptom score (TNSS). A p value of <0.05 was considered to indicate a significant difference.

Results

Characteristics of patients with PAR and controls

The characteristics of patients with PAR and controls are shown in Table 1. All children with PAR were sensitized to 3 species of mites: *B. tropicalis*, *D. pteronyssinus* and *D. farinae*, and these 3 mite species were the most common allergens. There was no significant difference in characteristics between patients aged 6 to 12 years and those aged below 6 years.

Relationships of allergic inflammatory markers with PAR severity

Results of bivariate correlation analysis of the relationships of AR severity with age and allergic inflammatory markers in children with PAR are shown in Table 2. All markers correlated with the severity of AR. Among them, SME1 was highly correlated, CAP2, serum total IgE and blood

Table 2. Relationship of allergic rhinitis severity to age and to allergic inflammatory markers in children with perennial allergic rhinitis (bivariate correlation analysis)

	Age	IgE	CAP1	CAP2	CAP3	ECP	EOS	SME1	SME2
R	0.123	0.382	0.203	0.510	0.464	0.242	0.365	0.789	0.556
p	0.122	<0.001[a]	0.010[a]	<0.001[a]	<0.001[a]	0.002[a]	<0.001[a]	<0.001[a]	<0.001[a]

Abbreviations: IgE = immunoglobulin E; CAP1 = positive number of allergen-specific IgE; CAP2 = maximum valence of allergen-specific IgE; CAP3 = sum of valence of allergen-specific IgE; ECP = eosinophil cationic protein; EOS = blood eosinophil count; SME1 = nasal eosinophil grade; SME2 = nasal eosinophil percentage
[a]$p<0.05$.

Table 3. Multiple linear regression analysis of total nasal symptom score including IgE, CAP1, CAP2, ECP, eosinophils and SME1

	Coefficients	Standard error	*p*
IgE	–0.00014	0.001	0.796
CAP1	0.0105	0.199	0.958
CAP2	0.601	0.213	0.005[a]
ECP	0.0089	0.011	0.401
Eosinophils	0.00067	0.001	0.439
SME1	3.210	0.265	<0.001[a]

Abbreviations: IgE = immunoglobulin E; CAP1 = positive number of allergen-specific IgE; CAP2 = maximum valence of allergen-specific IgE; ECP = eosinophil cationic protein; SME1 = nasal eosinophil grade

[a]$p<0.05$.

eosinophil count were moderately correlated, and serum ECP was minimally correlated.

The results of multivariate linear regression analysis, which included the variables IgE, CAP1, CAP2, ECP, eosinophils, and SME1 due to their significance in the univariate analysis ($p<0.05$), are shown in Table 3. Among these variables, only SME1 and CAP2 were independently correlated with TNSS. The regression equation was TNSS = ([2.331 – 0.00014] × IgE) + (0.0105 × CAP1) + (0.601 × CAP2) + (0.0089 × ECP) + (0.00067 × EOS) + (3.210 × SME1). The relationship of TNSS with CAP2 is shown in Fig. 1. The simple linear regression equation was: TNSS = 4.867 + 1.737 × CAP2. The relationship of TNSS with SME1 is plotted in Fig. 2. The simple linear regression equation was TNSS = 4.404 + 3.685 × SME1.

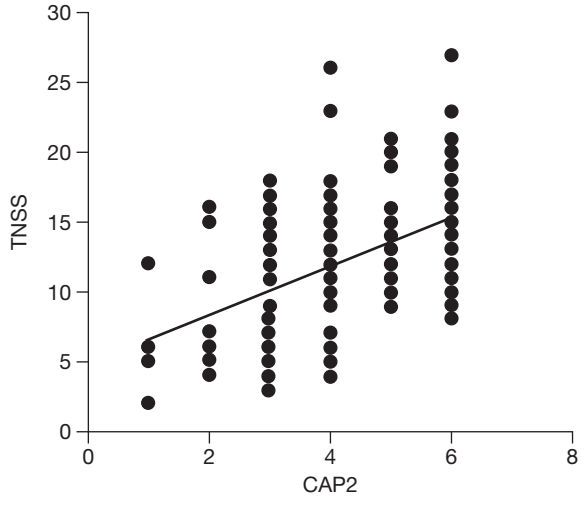

Fig. 1. Correlation between total nasal symptom score (TNSS) and maximum valence of serum allergen-specific immunoglobulin E (CAP2); R = 0.510, $p<0.001$.

Relationships among markers

The results of bivariate correlation analysis of the relationships among markers are shown in Table 4. Serum total IgE was moderately correlated with serum allergen-specific IgE, nasal eosinophil count and blood eosinophil count, and less correlated with serum ECP. Serum allergen-specific IgE was moderately correlated with serum total IgE, nasal eosinophil count and blood eosinophil count, and less correlated with serum ECP. Blood eosinophil count was moderately correlated with nasal eosinophil count, serum total IgE and serum allergen-specific IgE, and was not correlated with serum ECP. Nasal eosinophil count was moderately correlated with serum allergen-specific IgE, serum total IgE and blood eosinophil count, and less correlated with serum ECP. Serum ECP was minimally correlated with nasal eosinophil count, serum total IgE, and serum allergen-specific IgE, and was not correlated with blood eosinophil count.

Discussion

This study demonstrated that levels of all allergic inflammatory markers in children with PAR were significantly different from those in non-allergic children, except for serum ECP. These results are somewhat inconsistent with those of 3 previous studies which found that serum ECP levels in children with AR were significantly higher than those in controls [3,4,9]. These 3 studies, however, included fewer patients with AR (21, 49, and 71, respectively), and 1 of the studies also included patients with both rhinitis and asthma, which may have confounded the analysis [3]. By comparison, this present study had a larger sample of 160 patients.

Bivariate correlation analysis revealed that all markers of allergic inflammation were correlated with the severity of AR. In addition, comparison of analytical results for the number of positively reactive allergens, the highest valence among the 10 allergens tested, and the sum of the valences for serum allergen-specific IgE showed that all 3 were significantly correlated with the severity of AR. However, in multiple linear regression, the correlation with the highest valence among the 10 allergens was more than that for the number of positively reactive allergens ($p=0.005$ versus 0.958). Thus, valence was more strongly correlated with AR severity than the number of different positively reactive allergens, and the correlation was highest with a critical valence, i.e., the highest valence among the 10 allergens, and not with

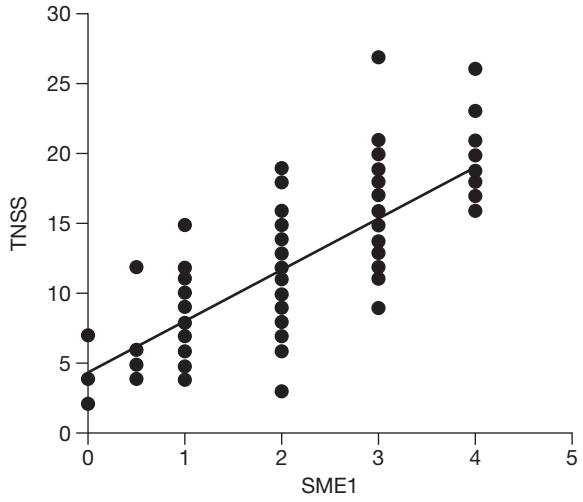

Fig. 2. Correlation between total nasal symptom score (TNSS) and nasal eosinophil grade (SME1), R = 0.789, $p<0.001$.

the sum of the valences of the 10 allergens. A similar evaluation for nasal eosinophil counts showed that both were well correlated with the severity of AR, while grading of the mean number of eosinophils per 10 high-power fields had a higher correlation coefficient.

Bivariate correlation analysis showed that markers of allergic inflammation were all mutually correlated. Among them, serum ECP was the least correlated, and was not correlated with blood eosinophil count. This may be attributable to the pathogenesis of AR, in which ECP is released from activated eosinophils which are accumulated in the local nasal mucosa. Theoretically, there is less correlation between ECP and blood eosinophil count.

The results of this study suggest that simple tests such as blood esoinophil count can provide useful information for diagnosis and prediction of severity of AR. However, on multiple regression analysis, only nasal eosinophil count and serum allergen-specific IgE were independent predictors of AR severity.

In 1979, Malmberg reported that nasal secretion eosinophilia was significantly correlated with AR history, nasal mucosa swelling and nasal secretion [12]. Similar results were subsequently reported in several

Table 4. Relationships between age, serum IgE, serum allergen-specific IgE, serum ECP, blood esosinophil count and nasal eosinophil count (bivariate correlation analysis)

	Age	IgE	CAP1	CAP2	CAP3	ECP	EOS	SME1
Age								
R	1.000	0.054	0.126	0.072	0.152	0.173	–0.027	0.124
p		0.497	0.111	0.368	0.055	0.028[a]	0.739	0.119
IgE								
R	0.054	1.000	0.408	0.557	0.596	0.181	0.353	0.435
p	0.497		<0.001[a]	<0.001[a]	<0.001[a]	0.022[a]	<0.001[a]	<0.001[a]
CAP1								
R	0.126	0.408	1.000	0.383	0.762	0.082	0.090	0.202
p	0.111	<0.001[a]		<0.001[a]	<0.001[a]	0.303	0.257	0.011[a]
CAP2								
R	0.072	0.557	0.383	1.000	0.842	0.172	0.342	0.465
p	0.368	<0.001[a]	<0.001[a]		<0.001[a]	0.027[a]	<0.001[a]	<0.001[a]
CAP3								
R	0.152	0.596	0.762	0.842	1.000	0.072	0.250	0.425
p	0.055	<0.001[a]	<0.001[a]	<0.001[a]		0.367	0.001[a]	<0.001[a]
ECP								
R	0.173	0.181	0.082	0.172	0.072	1.000	0.129	0.242
p	0.028[a]	0.022[a]	0.303	0.027[a]	0.367		0.104	0.002[a]
EOS								
R	–0.027	0.353	0.090	0.342	0.250	0.129	1.000	0.365
p	0.739	<0.001[a]	0.257	<0.001[a]	0.001[a]	0.104		<0.001[a]
SME1								
R	0.124	0.435	0.202	0.465	0.425	0.242	0.365	1.000
p	0.119	<0.001[a]	0.011[a]	<0.001[a]	<0.001[a]	0.002[a]	<0.001[a]	

Abbreviations: IgE = immunoglobulin E; CAP1 = positive number of allergen-specific IgE; CAP2 = maximum valence of allergen-specific IgE; CAP3 = sum of valence of allergen-specific IgE; ECP = eosinophil cationic protein; EOS = blood eosinophil count; SME1 = nasal eosinophil grade

[a]$p<0.05$.

studies [13-15]. However, Crobach et al's study of the predictive value of nasal smear eosinophilia for AR in 1996 showed that although it contributed significantly to the diagnosis of AR, this contribution was very small and was considered clinically irrelevant [23]. Due to this difficulty in differentiating whether a patient has AR using nasal smears alone, nasal smear eosinophilia study is not often performed in general practice. A recent study, however, concluded that eosinophil count in nasal scrapings was highly correlated with the clinical and immunological parameters in AR [18]. The results of this study that nasal eosinophil count has the lowest *p* value and highest R value among all allergic inflammatory markers confirm this finding.

It remains controversial whether serum allergen-specific IgE is useful in the diagnosis and assessment of severity of AR, with some studies supporting [4,6,7] and others negating its value [20,21]. However, in this study, both bivariate correlation analysis and multiple regression analysis found correlation between allergen-specific IgE and severity of AR. These findings suggest a significant role of aeroallergens in the induction of AR.

In conclusion, among the inflammatory markers serum total IgE, serum allergen-specific IgE, serum ECP, blood eosinophil count and nasal eosinophil count, only organ-specific nasal eosinophil count and systemic serum allergen-specific IgE were correlated with the severity of childhood PAR. The highest valence ranking of serum IgE for allergens was the key factor in correlation with the severity of PAR.

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