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The correlation of serum eosinophil cationic protein level with eosinophil count, and total IgE level in Korean adult allergic rhinitis patients

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Abstract

Background: Eosinophil cationic protein (ECP) is present in eosinophil granules. It has been associated with eosinophil-associated disorders.

Objective: We compared serum ECP levels in allergic and non-allergic rhinitis patients and evaluated the association with the eosinophil count and the total IgE level.

Method: We retrospectively reviewed medical records and categorized enrolled patients into the allergic (AR) and non-allergic rhinitis (NAR) groups. ECP, eosinophil count, and total IgE levels were reviewed in both groups. The association between ECP and the eosinophil count and total IgE level was further evaluated according to commonly detected specific antigens.

Results: Six hundred and ten adults were included in the study. In the AR group (n=349), the median age was 27.0 (23.0-42.0) years and the female:male ratio was 0.26:1. In the NAR group (n=261), the median age was 32.0(24.0-45.5) years and the female:male ratio was 0.33:1. We found that ECP (AR: 18.8(9.9-31.4), NAR: 14.8(8.2-24.9), p=0.003), eosinophil count (AR: 191.0(112.0-308.5), NAR: 149.0(91.0-249.0), p=0.002) and total IgE (AR: 166.0(58.4-422.5), NAR: 68.8(24.5-141.0), p<0.001) were higher in AR than in NAR patients. The ECP level was associated with the eosinophil count in both the AR (p<0.001) and NAR groups (p<0.001). A significant correlation between the ECP level and eosinophil count was demonstrated in AR patients who were skin test positive against house dust mite, animal and pollen allergens.

Conclusions: We suggest that ECP could be an important mediator in the pathogenesis of AR. The level of serum ECP was positively correlated with eosinophilia in AR patients regardless of the type of allergen sensitization. However, further study is warranted to verify the role of ECP in the clinical management of allergic rhinitis.

Keywords: eosinophil cationic protein, immunoglobulin E, eosinophil count, allergic rhinitis, MAST

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Introduction

Eosinophil cationic protein (ECP) is a single polypeptide chain comprising 133 amino acids, and is a ribonuclease 3.[1] ECP is present in eosinophil granules and can be secreted into the extracellular area in an antibody-dependent and antibody-independent manner. IgG and IgA induce antibody-dependent secretion of ECP, and complement components or cytokines induce antibody-independent secretion.[2,3] Many clinical conditions are associated with the amount of ECP secretion. Serum ECP levels are higher in patients suffering from chronic inflammatory respiratory disease compared to healthy volunteers.[4] Elevated serum ECP has also been reported in acute bacterial and viral infections.[5] The presence of nasal polyps is also associated with elevated serum ECP levels in chronic rhinosinusitis patients.[6]

As ECP originates from eosinophils (although small amounts can be found in neutrophils and monocytes), clinical conditions with pathogenesis mediated by eosinophils are typically associated with ECP.[1] In asthmatic patients, serum ECP has been found to be a potential marker, and the ECP level has been correlated with disease activity and severity.[7] In the upper airway, total serum IgE, ECP and the percentage of eosinophils are strong predictors of allergic rhinitis,[8] and nasal allergen provocation tests induce local production of ECP.[9] Serum ECP does not vary between local allergic rhinitis patients and non-allergic rhinitis patients or controls.[10] A recent study found that local ECP measured in sinus mucosa homogenates is significantly correlated with antigen-specific IgE levels in chronic patients with rhinosinusitis polyps.[11]

Compared to other atopic diseases, the study of serum ECP in allergic rhinitis remains limited.[12-16] We sought to evaluate the diagnostic value of ECP in allergic rhinitis, with regard to antigen specificity in allergic rhinitis patients.

Methods

Subjects

This study included a total of 610 patients with or without allergic rhinitis treated at a single institution from February 2009 to December 2012 (136 female and 474 male subjects aged 9-78 years). This study was approved by the Institutional Review Board of Chung-Ang University. Based on subjective symptoms, endoscopic findings, and the Multiple Allergen Simultaneous Test (MAST) for 39 antigens, patients were classified into allergic rhinitis (AR) and non-allergic rhinitis (NAR) groups. Patients who were diagnosed with sinusitis and other atopic diseases such as atopic dermatitis or asthma were excluded from our study. All patients were asked about their history of asthma or other atopic diseases, and patients who were diagnosed with asthma or were symptomatically suspected for asthma were excluded from our study.

Patients suspected for AR underwent blood tests including MAST, ECP and IgE levels, and eosinophil counts. Based on the serological results, patients who were negative for MAST were regarded as NAR. These patients might have vasomotor rhinitis and chronic rhinitis (NOS) according to the ICD10 definition (version 2016). We defined these patients as NAR patients.

Measurement of serum ECP, total IgE, and total eosinophil counts

All measurements were made at the Department of Laboratory Medicine at Chung-Ang University Hospital. Briefly, serum total IgE and ECP levels were assessed by the ImmunoCAP250 assay (Thermo Scientific, Waltham, MA, USA), and MAST was performed using the AlleRoboT system (Bee Robotics, Wales, UK). Serum total eosinophil counts were assessed using an XN9000 apparatus (Sysmex, Kobe, Japan).

Statistics

All statistical analyses were performed using software SPSS version 18.0 (SPSS, Inc., Chicago, IL). For continuous variables, the distribution of the data was first evaluated for normality using the Kolmogorov-Smirnov test. As all the variables did not pass the normality test, data were expressed as medians (P_{25}-P_{75}), and these data were analyzed using non-parametric tests. The Mann-Whitney test was used to compare the levels of total IgE and ECP as well as eosinophil counts between the AR and NAR groups. Spearman's correlation coefficient was calculated to evaluate the correlation between serum ECP, eosinophil counts and total IgE. Also, Spearman's correlation coefficient was calculated to evaluate the relationship between ECP, eosinophil count, and the total IgE level in each specific allergen-positive group. A probability level of $p<0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 610 patients were included in our study. Among them, 349 were diagnosed with AR, and 261 patients were diagnosed as NAR. The median age was 27.0(23.0-42.0) years in AR patients and 32.0(24.0-45.5) years in NAR patients; this difference was statistically significant ($p<0.05$). Males were predominant in both groups, but the sex difference was not statistically significant between groups. The serum total IgE level (normal range: 0-100 IU/ml) was 166.0(58.4-422.5) IU/mL in the AR group and 68.8(24.5-141.0) IU/mL in the NAR group ($p<0.05$). Serum ECP (normal range: <16 μg/mL) was 18.8(9.9-31.4) μg/mL in the AR group and 14.8(8.2-24.9) μg/mL in the NAR group ($p<0.05$). The blood eosinophil count (normal range: 0-300/μL) was 191.0(112.0-308.5) in the AR group and 149.0(91.0-249.0) in the NAR group ($p<0.05$). All of these values were significantly higher in AR patients compared to NAR patients (**Table 1**).

MAST results of enrolled subjects

We performed MAST for 39 allergens and reactions equal to or greater than class 2 (≥0.7 IU/ml) were considered positive. *Dermatophagoides farinae* (Df: 218/349, 62.5%) and *Dermatophagoides pteronyssinus* (Dp: 186/349, 53.3%) were the most frequently detected allergens. Patients also showed frequent positivity to pollens and cat dander. **Figure 1** shows the top 10 allergens in Korea. Also, the number of positive allergens in the AR group was checked (**Figure 2**), and the comparison of ECP, total IgE, and eosinophil counts between

Table 1. The characteristics of enrolled patients and the level of three parameters.

Parameters	Allergic rhinitis (N=349)	Non allergic rhinitis (N=261)	Statistics
Age, years	27.0(23.0-42.0)	32.0(24.0-45.5)	p=0.004
Sex			
Male (%)	278(79.65)	196(73.56)	p=0.108
Female (%)	71(20.34)	65(24.90)	
Total IgE, IU/mL	166.0(58.4-422.5)	68.8(24.5-141.0)	p<0.001
ECP, μg/mL	18.8(9.9-31.4)	14.8(8.2-24.9)	p=0.003
Eosinophils,	191.0(112.0-308.5)	149.0(91.0-249.0)	p=0.002

Abbreviation: IgE, Immunoglobulin E; ECP, Eosinophil cationic protein
Data are presented as median(P_{25}-P_{75}), or absolute number(%).
p<0.05, with statistical significance

Table 2. The level of ECP, total IgE, and eosinophil counts in AR group according to the number of positive allergen

	Number of positive allergen						
	One	Two	Three	Four	Five	Six	More than Seven
Number(%) (total=349)	89(25.5)	49(14.0)	87(24.9)	47(13.5)	23(6.6)	16(4.6)	38(10.9)
ECP	15.05 (7.33-24.60)	19.50 (11.65-29.90)	20.00 (10.70-29.40)	29.70 (12.00-50.50)	22.90 (11.60-44.50)	17.85 (11.23-32.88)	17.80 (9.72-34.50)
Total IgE	62.50 (31.33-159.00)	148.00 (52.05-331.50)	157.00 (61.60-274.00)	182.00 (108.0-410.00)	371.00 (142.00-609.00)	659.50 (299.00-1708.50)	497.50 (286.75-1107.00)
Eosinophils	151.50 (80.75-258.25)	227.00 (150.50-338.00)	181.00 (121.00-289.00)	218.00 (120.00-332.00)	200.00 (125.00-320.00)	199.00 (128.25-318.75)	224.00 (144.25-399.25)

Abbreviation: IgE, Immunoglobulin E; ECP, Eosinophil cationic protein; MAST, Multiple Allergen Simultaneous Test
Data are presented as median(P_{25}-P_{75}), or absolute number(%).

Table 3. Correlations of total eosinophil count and total IgE with serum ECP in AR and NAR groups

	Serum ECP			
Parameters	Allergic rhinitis		Non allergic rhinitis	
	r	p	r	p
Eosinophils	0.533	<0.001	0.576	<0.001
Total IgE, IU/mL	0.188	<0.001	0.069	0.265

Abbreviation: IgE, Immunoglobulin E; ECP, Eosinophil cationic protein
r, correlation coefficient; p<0.05, with statistical significance

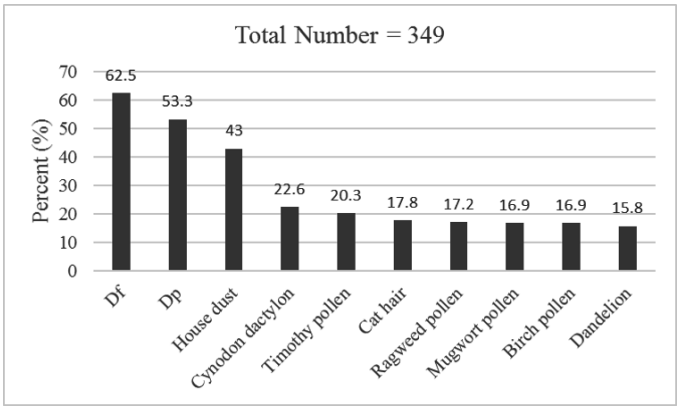

Figure 1. Top 10 Allergens positive MAST results in adult Korean AR group (N=349)

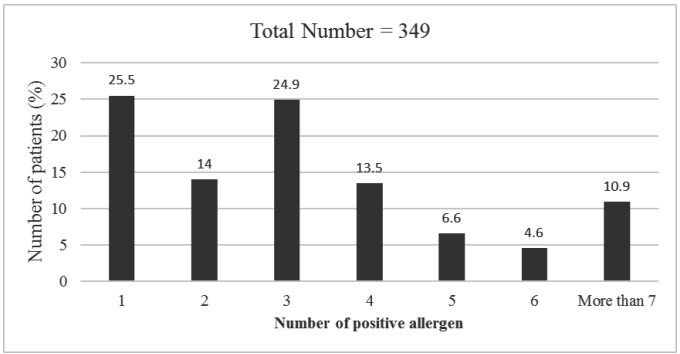

Figure 2. The number of patients according to the number of positive allergen in AR group (N=349)

Table 4. The level of ECP, total eosinophil count, and total IgE according to allergen species in AR group

Parameters	HDM only (N=88)	Pollen only (N=51)	Animal only (N=23)	p-value
Total IgE, IU/mL	158.0 (57.4-285.5)	93.6 (43.1-178.0)	73.7 (46.3-423.0)	0.029
ECP, μg/mL	22.2 (12.7-36.1)	14.1 (6.7-21.8)	12.8 (7.1-30.3)	0.093
Eosinophils	203.0 (121.3-301.8)	148.0 (800-229.0)	232.0 (71.0-358.0)	0.002

Abbreviation: HDM, house dust mite; IgE, Immunoglobulin E; ECP, Eosinophil cationic protein
Data are presented as median(P_{25}-P_{75}), or absolute number(%).
p<0.05, with statistical significance

Table 5. Correlations of total eosinophil count and total IgE with serum ECP according to allergen species in AR group

	Serum ECP					
	HDM only (N=88)		Pollen only (N=51)		Animal only (N=23)	
	r	p	r	p	r	p
Eosinophils	0.590	<0.001	0.423	0.002	0.583	0.003
Total IgE, IU/mL	0.141	0.791	0.038	0.790	0.382	0.070

Abbreviation: HDM, house dust mite; IgE, Immunoglobulin E; ECP, Eosinophil cationic protein
r, correlation coefficient; p<0.05, with statistical significance

groups was performed. The levels of these three parameters in AR patients did not increase as the number of positive allergens detected by MAST increased (**Table 2**). Therefore, we chose house dust mite (HDM), pollens and animals as the three most common allergens, and divided patients into three groups: house dust mite-only positive (n=88), pollen-only positive (n=51), and animal-only positive (n=23, cat hair, dog hair and cockroach) to evaluate the relationship between ECP, the eosinophil count, and total IgE level in each specific allergen-positive group.

Correlation of the total eosinophil count and total IgE with serum ECP

We compared the correlation between serum ECP and the eosinophil count. In both the AR and NAR groups, the level of serum ECP was positively correlated with the eosinophil count ($p<0.05$). When we evaluated the relationship between serum ECP and the serum total IgE level, the correlation was statistically significant in the AR group ($p<0.05$), but not statistically significant in the NAR group (**Table 3**).

When we evaluated the correlations among these three parameters according to specific allergens, a total of 162 patients were positive for either HDM, pollen or animal allergens. Among these 162 patients, 88 were positive for HDM only, 51 were positive for pollen only, and 23 were positive for animal only. Median total IgE level was highest in the animal-only group ($p<0.05$). Median ECP ($p>0.05$) level and median eosinophil count ($p<0.05$) were higher in the HDM-only group compared to the pollen-only and animal-only groups (**Table 4**). When the correlation of ECP with the eosinophil count and total IgE level was calculated, ECP was positively correlated with the eosinophil count in all three groups; the coefficients of correlation in all three groups were above 0.4, which indicates a relatively strong correlation. However, there were no correlations between ECP and the total IgE level in any of the three groups.

Discussion

Although many researchers have evaluated the serum ECP level as a marker of various atopic diseases, investigations into the correlation between ECP and AR have been relatively sparse. Although some studies have reported an association between serum ECP and the occurrence of AR, other studies have failed to find a similar association.[17,18] Our study, which is based on a relatively large number of adult subjects, found that serum ECP was higher in AR patients and was correlated with the blood eosinophil count in both AR and NAR patients. As eosinophilic inflammation is a common feature of allergic disorders, the eosinophil count is typically representative of the severity of allergic disease.[19] Our findings suggest that an elevated serum ECP level is closely associated with the eosinophil count and serum ECP may play a role as a diagnostic marker in adult AR patients. Interestingly, we found that the level of serum ECP was also correlated with the total eosinophil count in non-AR patients. Not only ECP, but also proteins such as major basic protein (MBP) and eosinophil-derived neurotoxin are present in the cytoplasm of eosinophils.[5] Based on prior studies, the role of these proteins in each organ system may be distinct. Serum MBP has been identified as a potential marker of disease activity, showing a close correlation with the clinical score in atopic dermatitis patients.[20] However, ECP, but not MBP, is higher in atopic keratoconjunctivitis, and the level of ECP has been correlated with corneal staining and conjunctival injection scores, suggesting that ECP is a marker of disease severity.[21] In our study, the level of ECP in non-AR patients was higher than it was in non-asthmatic patients, while the level of ECP in AR patients was similar to that of asthmatic patients.[22] Our findings suggest that ECP might be a major eosinophil protein in upper respiratory tract inflammatory disease.

In the present study, serum total IgE level was higher in AR patients compared to NAR patients. Total serum IgE levels in AR and NAR patients were similar to the results of previous reports focused on another atopic disease, allergic asthma.[8] Unexpectedly, we found that total serum IgE was significantly associated with serum ECP in AR patients, although this association disappeared when further evaluated according to single allergen positivity. In a previous study, it was found that the total serum IgE level was not correlated with the severity of atopic disease.[23] No correlations between serum IgE and ECP levels have been found in children with asthma or urticaria.[22,24] However, in adults, the serum total IgE level was found to be a strong predictor of AR in a previous report.8 Limited and inconsistent data regarding the role of serum total IgE as a marker in the diagnosis and severity of AR suggests that further evaluation of this topic is needed in studies that assess age, sex, and allergen species as variables.

Previously, it was established that patients challenged with an allergen show a rapid initial rise in the serum ECP level, followed by a very rapid reduction. Serum ECP levels are unexpectedly low in asthmatic patients.[25,26] Therefore, we hypothesized that the serum ECP level might vary according to specific allergens. Serum ECP was highest in the HDM-only group, and lowest in the pollen-only group. We theorize that seasonal pollen allergens might cause a rapid rise and reduction in the ECP level in AR patients, while HDM or animal allergens, which are perennial allergens, might cause a continuous rise in the ECP level. The change in serum ECP levels according to specific allergen groups might be another interesting area of further investigation.

Although serum ECP had the strongest association with eosinophil count in the HDM-only group, the coefficients of correlation between serum ECP and the eosinophil count according to allergen species were 0.590 (HDM only), 0.583 (animal only) and 0.423 (pollen only); there were no statistically significant differences among the three groups (**Table 5**). Based on our findings, we suggest two important points. First, we suggest that the role of ECP and eosinophils in AR might vary by allergen, and that ECP might be an important biomarker of AR adult patients regardless of allergen species. Second, we suggest that ECP may be a major eosinophilic granular protein in upper airway inflammation because serum high ECP levels were associated with the occurrence of both AR and NAR and was positively correlated with the eosinophil count in both AR and NAR.

The novelty of our study is that we enrolled a large number of adult patients, while previous studies have mainly focused on children. However, our study has some limitations. First, we did not evaluate the subjective symptoms of enrolled patients, or their correlation with ECP. Second, we only measured the systemic ECP level, not the local ECP level. In addition to systemic ECP, local ECP has been found to be associated with the pathogenesis of atopic diseases.[27] For example, in atopic keratoconjunctivitis patients, local tear ECP levels are higher compared to those of normal subjects, and correlated with disease severity.[21] Third, we did not separately analyze seasonal and perennial allergens. Therefore, in seasonal AR-only or perennial AR-only patients, different results may be

observed. Fourth, we did not perform a follow-up assessment of the levels of IgE and ECP, or the eosinophil count, so we cannot speculate on changes in these parameters. Moreover, we did assess if treatment may have affected these allergic parameters. Finally, the number of patients sensitive to only one specific allergen was small. Thus, further large-scale studies may be needed.

Conclusion

We suggest that ECP could be an important mediator in the pathogenesis of AR. The level of serum ECP was positively correlated with eosinophilia in AR patients regardless of the type of allergen sensitization. However, further study is warranted to verify the role of ECP in the clinical management of AR.

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None.

Competing interests

None declared.

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