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Eosinophil Cationic Protein in Chronic Urticaria

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Abstract

Background: Eosinophil Cationic Protein (ECP) is a well-known activity indicator in allergic disease. Recently eosinophils have drawn attention as a major source of tissue factors in chronic urticaria. However, there have been few reports on significance of serum ECP in chronic urticaria.

Aims: To evaluate the clinical significance of serum ECP in chronic urticaria and clarify the relationship between serum total IgE and ECP in a severity index.

Methods: The retrospective chart review was performed on 114 patients with chronic urticaria. Serum ECP and total IgE were measured before treatment. The treatment period required to improve clinical symptoms with two different kinds of oral antihistamines twice a day was checked and the relationship between the treatment period and serum ECP and total IgE levels were evaluated.

Results: Patients showing high ECP level before treatment need more time to manage their urticarial symptoms than those with low ECP level ($p=0.018$). However, there were no significant differences between treatment period and serum total IgE level ($p=0.543$). Serum ECP and total IgE was moderately correlated with each other (r=0.200, $p=0.041$).

Conclusions: Serum ECP can be a better indicator of disease severity in chronic urticaria than IgE. The patients showing high ECP level from the beginning require relatively longer period for symptom relief and can be helped by more than two kinds of oral antihistamines.

Keywords: Chronic urticaria; Eosinophil cationic protein; Total IgE

Introduction

Chronic urticaria, as well as atopic dermatitis, asthma, and allergic rhinitis is a representative disease mediated by IgE. Mast cells and basophils were previously known as main effector cells in chronic urticaria. However, recent studies are paying their attention to eosinophils and their roles in producing tissue factors in chronic urticaria [1].

The role of Eosinophil Cationic Protein (ECP) is well documented in atopic dermatitis, asthma and allergic rhinitis patients [2,3]. ECP is a cytotoxic agent secreted by activated eosinophils during allergic or inflammatory process and has been examined in various allergic disorders as an activation marker. However, there have been few reports about serum ECP and its clinical significance in patients with chronic urticaria. With this background, we evaluate serum ECP and total IgE as a severity index in chronic urticaria patients.

Materials and Methods

Study population

Under the approval of Institutional Review Board of Seoul National University Boramae Hospital, retrospective review of medical records was conducted on patients who visited our clinic from March 2009 to August 2011 and were diagnosed as chronic urticaria. A total of 119 patients (76 female and 43 male: mean age 39.0 ± 17.1 years) were included in this analysis. At the time of presentation, all patients did not show urticarial wheals. Therefore, the diagnosis was made on the basis of patients' history of appearing continuous or recurrent hives with or without angioedema for more than 6 weeks. Patients with urticarial vasculitis, leukocytoclastic vasculitis, physical urticaria and previous and/or present atopic dermatitis were excluded. Patients were divided into two groups, based on serum ECP level (serum ECP > 18 ng/ml: high ECP group versus serum ECP < 18 ng/ml: low ECP group). In addition, they were also grouped into two, based on serum total IgE level (IgE > 183 IU/ml: high IgE group versus IgE < 183 IU/ml: low IgE group) (based on the normal range of ECP and total Ig E provided by laboratory test).

Monitoring of disease activity parameter

The patients all underwent a panel of basic investigations including routine blood test, erythrocyte sedimentation rate, anti-nuclear antibody, serum ECP, and total IgE (+/- MAST panel) before treatment. At the time of blood sampling, they were off any previous oral antihistamines or glucocorticoids for at least 1 week. Patients were prescribed two different kinds of oral antihistamine twice a day, after the blood sampling. They were scheduled to revisit the clinic in 2 weeks and later on, they were followed every 2 to 4 weeks. They were not prescribed oral glucocorticoids.

The time required to improve urticarial symptoms with two different kinds of oral antihistamines after the initial blood test was documented in all patients (meaning once a day medication of one kind of oral antihistamine is enough to suppress urticarial wheal during a day without itching sensation).

Statistical analysis

Student's t-tests were performed between each group. Correlation

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coefficients were determined by Pearson's rank correlation test. All data were analyzed using SPSS 18.0K for window. Data are expressed as mean ± SEM and *p-value* less than 0.05 was considered statistically significant.

Results

ECP level and treatment period

One hundred and fourteen patients were divided into two groups, 61 patients in high ECP group (ECP > 18 ng/ml, mean age: 40.3 ± 15.5 years) and 53 patients in low ECP group (ECP < 18 ng/ml, mean age: 35.9 ± 17.3 years). The time to take for managing urticarial symptoms with two different kinds of oral antihistamines twice a day in high ECP group was 5.84 ± 7.58 weeks and it is significantly longer compared with low ECP group (3.26 ± 3.19 weeks, *p=0.018*) (Figure 1).

Total IgE level and disease severity

Total IgE was measured in 110 patients out of 119 patients. Twenty-seven patients revealed high IgE level (total IgE > 183 IU/ml, mean age: 37.3 ± 17.3 years) and 83 patients had low IgE level (total IgE < 183 IU/ml, mean age: 41.1 ± 16.3 years). The time to take for managing urticarial symptoms by two different kinds of oral antihistamines was 5.56 ± 6.55 weeks in high group and 4.71 ± 6.16 weeks in low group. There was no significant difference between two groups (*p=0.543*, Figure 1).

Serum ECP and total IgE

ECP and total IgE was tested in 105 patients. Serum ECP and total IgE was found out moderately correlated (r=0.200, *p=0.041*, Figure 2).

Discussion

Chronic urticaria is a common skin disorder characterized by the recurrent eruption of short-lived wheals accompanied by redness and itching for at least 6 weeks. Chronic urticaria is considered as an autoimmune disease with the presence of circulating histamine releasing autoantibodies mainly directed against the high affinity IgE receptor FcεRI on mast cells and basophils or against IgE [4-7]. However, these autoantibodies appear in less than 50% of chronic urticaria cases.

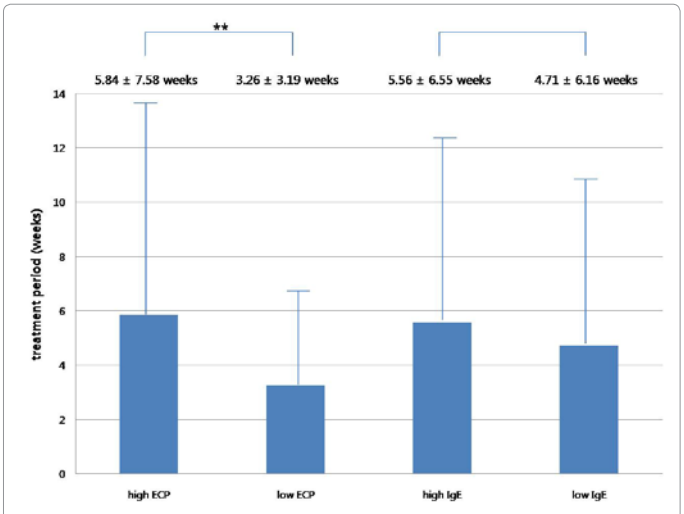

Figure 1: It takes significantly longer time for patient with high serum ECP level (5.84 ± 7.58 weeks) than those with serum low ECP level (3.26 ± 3.19 (weeks), *p=0.018*) to cut down their antihistamine mediation from twice a day with two different kinds to once a day with one kind of oral antihistamines. However, there was no significant difference between treatment period and serum Ig E level (*p=0.543*).

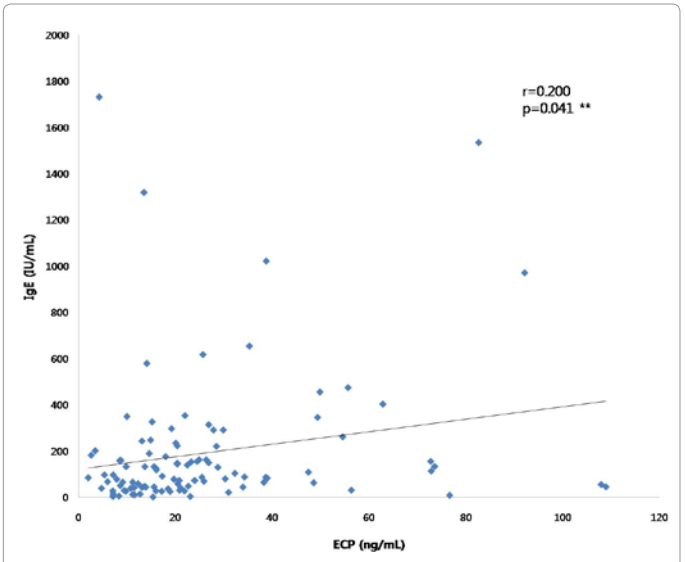

Figure 2: The serum level of ECP and total IgE was moderately correlated.

Recently, some evidences of possible involvement of the coagulation cascade in the pathogenesis of chronic urticaria have emerged. By activation of the tissue factor (TF) pathway, thrombin is generated and causes a relevant increase in vascular permeability [8,9] and activates mast cells, triggering their degranulation [10,11]. In one of those studies, immunohistochemical experiments showed TF expression in skin specimens from chronic urticaria patients [12]. It has been shown that eosinophils are the major intravascular source of TF, which is mainly embodied within their specific granules and is rapidly exposed by cell-specific stimulation [13]. Cugno et al reported the skin specimens from patients with chronic urticaria clearly demonstrated TF expression and they performed the double-staining experiments for TF and eosinophil cationic protein, showing that the TF-positive cells were eosinophils [1].

As discussed above, eosinophils are gaining new attention in the pathophysiology of chronic urticaria. Eosinophil cationic protein (ECP), one of the eosinophil granule proteins is considered useful indicator of eosinophil activity. In previous studies, the mean ECP serum concentrations were significantly higher both in patients with acute urticaria and chronic urticaria, compared to those of the healthy subjects [14]. Since blood eosinophil number does not exactly reflect the number of activated eosinophils that can release ECP [15], ECP level is more useful than blood eosinophil count itself. Atopic dermatitis, allergic asthma and rhinitis are well known IgE mediated disease and serum ECP level in these allergic disorders was thoroughly investigated as a disease severity indicator. This study demonstrated that patients with higher serum ECP level at the initial status required longer time to suppress their urticarial activity and it implicates that serum ECP level could reflect the status of disease activities in chronic urticaria patients.

This study was performed using retrospective chart reviews. Therefore, it has inevitable limitations. When considering clinical severity in urticarial patients, urticarial severity score is the most frequently used index [16]. However, we cannot infer the severity index based on urticaria severity score. At the time of examining patients, urticarial wheals were not observed in all patients. These

symptoms were obvious and worse in the evening and at night when patients were at home. Therefore, we checked the treatment period time during which patients had to be on two different kinds of oral antihistamines until these symptoms were controllable with only one kind of oral antihistamine once a day. With this data, we indirectly evaluated the clinical severity of patients. Patients showing high ECP before treatment tend to need more time to lessen their symptoms with oral antihistamines in this study. Autologus serum skin test is another frequently used method to predict the disease severity in chronic urticaria [17]. However, only 28% of chronic urticarial patients showed positivity of autologus serum skin test, which is too low to predict the patients' disease severity [16].

In this study, no significant correlation between treatment period and serum total IgE level was noticed. Some authors found a significant association between them, though [18]. This association may be explained by the effect of IgE on mast cell activation and degranulation. Lemanske and Kaliner reported the serum IgE level could be normal in allergic disease because of the short half-life of serum IgE [19]. The half-life of IgE is only 2.5 days in blood, but it can remain much longer in the skin as attached to basophils and mast cells. When small amount of IgE is produced, most IgEs bind to cells and is rarely released into the blood. Therefore, the clinical interpretation of serum total IgE level in allergic disorders can be sometimes obscure. The relationship between serum ECP and total IgE varies according to several studies [20]. In allergic rhinitis and asthma patients, the positive correlation of these two was noticed [20]. However, another report suggested there was no correlation between serum ECP and total IgE in acute and chronic urticaria, suggesting another possible stimulus for ECP release [21]. This study showed positive correlation between serum ECP and total IgE in chronic urticaria. However, the strength of this correlation was noticed rather weak. Considering those facts and our results, serum ECP level can be more useful in predicting activity and severity of chronic urticaria than serum IgE.

Conclusion

In summary, ECP may reflect disease activity and severity in chronic urticaria and may be helpful to predict treatment outcome. Patients, who show high ECP level, need longer period and require more than two kinds of oral medication at the frequent intervals in a day. This finding elicits the role of eosinophils in the pathophysiology and might push the right way for new therapeutic strategies of chronic urticaria.

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