

Correlation of Quality of Life with Clinical Parameters and Eosinophilic Cation Protein Levels in Children with Allergic Rhinoconjunctivitis

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Key Words

Allergic rhinoconjunctivitis · Eosinophilic cationic protein · Pediatric rhinoconjunctivitis quality of life questionnaire

results may indicate the absence of a correlation between clinical status and quality of life and levels of ECP in tissues with allergic inflammation.

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Abstract

Background: Systemic and mucosal roles of eosinophils in the pathogenesis of allergic rhinoconjunctivitis (AR) are known. The aim of this study was to investigate the relationship of clinical parameters and quality of life with eosinophilic cationic protein (ECP) in grass pollen-sensitive children with seasonal AR. **Methods:** This study included 31 children with AR and 18 healthy controls aged between 5 and 15 years. ECP levels in nasal lavage fluid and serum were measured. AR symptom scores were calculated and the pediatric rhinoconjunctivitis quality of life questionnaire (PRQLQ) was filled in for all patients. **Results:** Mean serum and nasal ECP levels (ng/ml) were significantly higher in the patient group ($p < 0.05$ for both). In the AR group, the mean clinical symptom score was 7.3 ± 2.2 , while the total PRQLQ score, activity limitation, symptoms and emotional function domains were 2.5 ± 0.9 , 3.0 ± 1.1 , 2.5 ± 1.2 and 2.6 ± 1.1 , respectively. The total clinical symptom score and disease duration showed a significant correlation with the total PRQLQ score ($p = 0.00$ and 0.003 , respectively). However, neither nasal lavage nor serum ECP levels were significantly correlated with symptom score, duration of disease, PRQLQ total score or domains ($p > 0.05$ for all). **Conclusion:** These

Introduction

Allergic rhinoconjunctivitis (AR) is the most common allergic disease with a prevalence of 5–40% and one of the leading chronic diseases in children [1–3]. Clinical findings of AR include nasal itching, sneezing, rhinorrhea, nasal congestion and conjunctival symptoms [4]. Allergic rhinitis is commonly associated with allergic conjunctivitis characterized by tearing, ocular itching and burning [5]. Nearly 92.5% of patients with allergic conjunctivitis have been reported to have coexisting AR [5].

Allergic rhinitis symptoms may have a negative impact on physical, psychological and social aspects of life, and therefore, influence the performance and wellbeing of children [6–8]. Limitations differ in different age groups; for example, being unable to play on grass may be a limitation for a child [9]. One of the most important end result is a decrease in health-related quality of life (HRQL) [7, 8]. HRQL can be defined as the patient's perception of functional effects of an illness and its treatment [9]. This approach is consistent with the definition of health stated by the World Health Organization as 'a state of complete

physical, mental and social wellbeing' [6]. Therefore, it has been proposed that HRQL needs to be included in the measurement of disease severity and outcome [2, 7]. HRQL can be evaluated by generic or disease-specific instruments [6, 7]. The pediatric rhinoconjunctivitis quality of life questionnaire (PRQLQ) has been developed to evaluate HRQL in children with rhinitis [10].

AR is induced by an IgE-mediated inflammatory reaction following allergen exposure and is characterized by eosinophil infiltration and degranulation [4, 11, 12]. Eosinophil-derived mediators including eosinophilic cationic protein (ECP) damage the epithelium leading to the final clinical and pathological AR findings [1, 13, 14]. It has been reported that mucosal allergic activity is correlated with serum and local mucosal ECP levels [12]. However, the relationship between levels of inflammatory cells or markers with clinical severity is controversial [4]. Still, good clinical outcome should include both symptom relief and an increased quality of life score [7, 15].

Although ECP may be related to clinical activity as a marker, its relationship to quality of life is unclear. The aim of this study was to clarify the relationship of clinical parameters and quality of life with ECP that is a marker of systemic and local inflammation.

Methods

Study Population

This study included 31 children with seasonal AR (23 males and 8 females) and 18 healthy controls (12 males and 6 females) aged between 5 and 15 years that presented to our department between March and July 2006. The diagnosis of seasonal AR depended on clinical findings of nasal itching, sneezing, nasal congestion and rhinorrhea. The patients were diagnosed to have grass pollen allergy detected by skin prick test (Allergopharma Ltd., Reinbek, Germany). Skin prick tests were performed according to the European Academy of Allergology and Clinical Immunology guidelines [16]. None of the children included in the study had received treatment for AR such as antihistamines or topical nasal steroids during the previous month. Moreover, none of the children had been diagnosed to have a psychiatric disease.

Healthy controls included in the study were recruited from the general pediatric outpatient department who had presented for healthy child follow-up. Children included in this group were especially questioned for AR symptoms and did not report to have any. Skin prick tests were also negative.

The families of all children gave consent to be included in the study.

Exclusion criteria included treatment with antihistamines or nasal steroids during the previous week, sensitization to allergens other than grass pollen, having a psychiatric disease, or declining to be included in the study.

Study Design

Demographic characteristics of children including age and sex were recorded at the beginning of the study. Then, the children were asked to score their nasal symptoms via the T4SS. Moreover, all children filled in the PRQLQ. Serum samples and nasal lavage fluid were obtained for measurement of ECP levels at the same time with recording of symptoms and PRQLQ.

The study was approved by the Ethical Committee of Celal Bayar University Hospital.

Symptom Score

T4SS is a subjective scoring system for the determination of symptom severity in patients with AR. It includes nasal itching, ocular itching, sneezing and nasal discharge that are scored from 0 to 3 with increasing severity. 0 indicates none, while 3 indicates severe symptom. The total score is calculated by adding the scores for all 4 domains.

Pediatric Rhinitis Quality of Life Questionnaire

The PRQLQ is a disease-specific quality of life questionnaire that has been developed by Juniper et al. [10]. It has 23 items grouped into 3 domains (symptoms, emotional function and activity limitations). Individual items within the PRQLQ are equally weighted. Each of the items has 7-point response (Likert type) scales, ranging from 0 to 6, where higher scores indicate greatest impairment. Domain scores are expressed as the mean score per item for each of the domains as well as for the overall quality of life score. The overall quality of life score is calculated by the mean score of all the items and not from the mean of the domain scores.

Nasal Lavage

Nasal lavage was performed while the patients were seated with the head tilted back. Then, an 8-french feeding catheter was inserted into 1 nostril, around 3 cm, and 10 ml of warm saline was introduced. The patient tilted the head forward and a plastic cup was held below the nostrils. The fluid that dripped out of the nostrils was collected into the plastic cup. The procedure was repeated for the other nostril. This yielded around 5–7 ml of fluid which was immediately given to the laboratory for measurements. Centrifugation was performed at 1,200 g for 10 min [12, 17].

Serum Samples for Measurement of ECP

Serum samples for in vitro measurement of ECP were obtained from all children after 8 h of fasting. Venous blood samples of 2 ml were obtained and left to clot for 60 min in room temperature. They were centrifuged for 10 min at 1,200 g. Serum samples were stored at –20°C.

Measurement of Serum and Nasal Lavage Fluid ECP

In both specimens, levels of ECP were measured via the chemiluminescent enzyme immunoassay method at Immulite 2000 automated analyzer (Immulite 2000, DPC, Los Angeles, Calif., USA) with immulite ECP (DPC).

Statistical Analysis

Statistical analyses were performed by the SPSS 11.0 (Chicago, Ill., USA) computer program. Age means, serum and nasal levels of ECP in the 2 groups were compared with the Mann-Whitney

Table 1. Nasal and serum ECP levels in the AR and control groups

	AR group	Control group	p
Nasal ECP, ng/ml	24.5 ± 20.9	4.7 ± 4.9	<0.01
Serum ECP, ng/ml	49.0 ± 35.6	12.5 ± 7.9	<0.05

Table 2. The total PRQLQ score and domain scores in patients with AR

	Score
Total PRQLQ score	2.5 ± 0.9
Activity limitation domain score	3.0 ± 1.1
Symptom domain score	2.5 ± 1.2
Emotional function domain score	2.6 ± 1.1

Table 3. Correlation of the total PRQLQ score and domain scores with the symptom score and disease duration

	Total symptom score		Disease duration	
	r	p	r	p
Total PRQLQ score	0.68	0.00	0.52	0.003
Activity limitation domain score	0.59	0.000	0.44	0.01
Symptom domain score	0.54	0.002	0.48	0.007
Emotional function domain score	0.73	0.000	0.47	0.007

U test. Pearson's correlation test was used to correlate disease duration, symptom score, nasal and serum ECP levels and PRQLQ scores. p values <0.05 were regarded as statistically significant.

Results

Patient Characteristics

The mean age of the AR group was 11.0 ± 2.7 years, while that of the control group was 9.3 ± 3.5 years. The age means of the 2 groups were not significantly different (p = 0.087).

Comparison of ECP Levels in the 2 Groups

The serum level of ECP in the AR group was significantly higher than that in the control group (49.0 ± 35.6 vs. 12.5 ± 7.9 ng/ml; p < 0.05). Similarly, nasal ECP levels

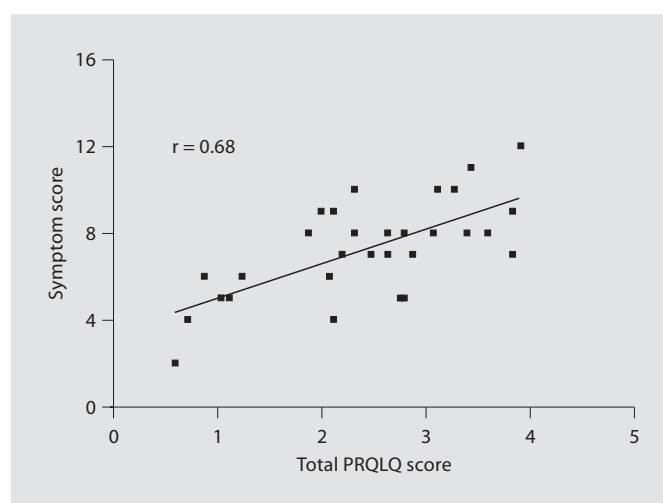


Fig. 1. Correlation of the total PRQLQ score and the symptom score.

were significantly higher in the AR group as well (24.5 ± 20.9 vs. 4.7 ± 4.9; p < 0.01) (table 1).

PRQLQ Scores

The total PRQLQ score in the AR group was 2.5 ± 0.9, while those of the activity limitation, symptoms and emotional function were 3.0 ± 1.1, 2.5 ± 1.2 and 2.6 ± 1.1, respectively (table 2).

Correlation of PRQLQ Scores with Disease Severity Parameters and ECP Levels

The symptom score and disease duration were significantly correlated with total and domain scores of the PRQLQ (p < 0.01 for all) (table 3; fig. 1). However, the nasal ECP level was not significantly correlated with the symptom score, disease duration or the PRQLQ total score (r = 0.04, 0.08 and 0.16, respectively; p > 0.05). Activity limitation, symptom and emotional function domain scores of the PRQLQ were not significantly correlated with nasal ECP levels either (r = 0.13, 0.31 and -0.09, respectively; p > 0.05). Similarly, serum ECP was not correlated with symptom score, disease duration or PRQLQ scores (p > 0.05).

Discussion

Allergic diseases are highly prevalent throughout the world and exert an important and socioeconomic burden because they interfere with many aspects of daily life [6].

Determination of patients' subjective perceptions gives a more realistic description of the impact of the disease on the patients' lives [6, 7]. HRQL can be evaluated by generic or disease-specific instruments [6, 7]. Generic measures are important in the overall assessment of HRQL [7]. On the other hand, specific measures focus on the influence of a specific disease and can detect small differences in the outcome related to that specific disease [6]. The PRQLQ that was developed to evaluate the HRQL in children with AR was used in this study.

Tissue infiltration of eosinophils is characteristic of allergic diseases [12]. The early phase of AR involves IgE-coated mast cells that traverse the epithelium and degranulate, leading to the production of mediators including histamine, tryptase, chymase, kininogenase, heparin and other enzymes in addition to inflammatory mediators that result in mucosal edema and rhinorrhea [1]. On the other hand, the late phase of AR involves infiltration of mucosa with eosinophils, neutrophils and basophils that results in congestion [1]. Eosinophils contain preformed cytoplasmic granules including major basic protein and other mediators that are synthesized such as leukotriene C₄, platelet-activating factor, tumor necrosis factor, transforming growth factor- β and interleukin 5 [13, 14]. Eosinophil-derived mediators such as major basic protein, eosinophilic cationic protein and leukotrienes damage the epithelium leading to the final clinical and pathological AR findings [1, 13, 14]. Similarly, it has been shown in our study that both serum and nasal levels of ECP are increased in children with AR when compared with the healthy controls. This is expected when the role of ECP is considered in the pathogenesis of AR. Similar to our findings, ECP was found to be increased in nasal lavage fluid of patients with seasonal AR during the pollen season [12]. It has been shown in previous studies that ECP levels in nasal lavage fluid of patients with AR is higher than that of the patients without AR [18]. Moreover, ECP levels were found to change in the pollen season and with immunotherapy in these patients [18, 19].

Allergic rhinitis negatively influences the patient's life both due to its symptoms like nasal obstruction, sneezing and itching and due to its influence on HRQL and sleep quality [15]. In children with AR, HRQL of both the parents and the child is affected including the ability to learn [6]. Adolescents with AR report difficulties, especially with concentration [7]. Children may experience emotional disturbance because they cannot fully integrate with their peers [9]. All the above problems attributed to AR may lead to behavioral problems [9]. Patients with AR report impairment in daily activity performance, work

productivity and classroom activities [7]. Allergic rhinitis does not have an impact only on psychological status but also on mood and cognition [7]. It has been demonstrated that children with AR have learning deficits, distraction, fatigue and irritability, all of which can deteriorate school performance [7, 9, 20].

However, the relationship between levels of inflammatory cells or markers with clinical severity is controversial [4]. A previous study has reported that serum levels of IgE, allergen-specific IgE, ECP and nasal eosinophil count were correlated with disease severity in patients with perennial AR [4]. On the contrary, our results demonstrated that markers of inflammation failed to significantly correlate with HRQL or subjective disease severity assessment in children with AR. Since HRQL depends on the patient's perception, a given severity of symptoms has a different influence on HRQL because the patient's sensitivity to specific areas of impairment differs [9]. Therefore, it is not surprising to detect that there is only a weak to moderate correlation between clinical measures and HRQL which was consistent with our findings [7, 15]. This emphasizes the importance of incorporation of HRQL measurement into the clinical evaluation of patients [7]. It is important both during initiation of therapy and during evaluation of the outcome of therapy [7]. It has been suggested that even a small change in HRQL is clinically significant because it is subjective [7]. A patient's HRQL cannot be predicted only on the basis of the disease severity [6]. On the other hand, in our study, the symptom score was significantly correlated with HRQL. This was attributed to the fact that the symptom score depended on subjective evaluation of children. Therefore, this aspect is especially important for allergic diseases because treatment aims to maximize functioning in everyday life [6].

The aim of treatment in AR is to achieve both a decrease in clinical findings and an improvement in HRQL. Although first-generation antihistamines may impair some aspects of HRQL due to their sedative effects, second-generation antihistamines do not cause significant sedation [9]. Therefore, it has been proposed that reduced learning ability and classroom performance associated with AR is reversed by treatment with second-generation but not with first-generation antihistamines [9, 21]. Not only antihistamine treatment but also nasal corticosteroids improve HRQL in AR by decreasing congestion [9]. Considering the results of our study, it is essential to include HRQL measurement in the assessment of therapy results because it does not correlate with clinical markers of inflammation.

In conclusion, both serum and nasal ECP is increased in patients with AR as expected for a marker of allergic inflammation. However, the levels of this marker are not correlated with subjective assessment of disease severity

or HRQL. These findings emphasize the importance of subjective assessment of HRQL such as the PRQLQ in the evaluation of children with AR along with objective inflammatory markers.

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