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ASTHMA AND EOSINOPHILIC CATIONIC PROTEIN AS AN INDICATOR OF DISEASE CONTROL

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SUMMARY – Asthma is the most common chronic disease in children and adolescents. It is necessary to develop objective methods for assessment of disease activity, treatment efficacy, and prevention of attacks. Measurements of eosinophilic cationic protein (ECP) should serve as an objective indicator of allergic inflammation activity. This follow-up study included 100 children treated with inhaled corticosteroid (fluticasone propionate) or sodium cromoglycate over a 12-month period. The values of (ECP) and forced expiratory volume in the first second (FEV1) were measured at the beginning of the study and then once a month for a year, to evaluate treatment efficacy. The fastest drop in ECP values and the highest increase in FEV1 were found in children with newly diagnosed asthma, who were treated with inhalation corticosteroid. This result supports the importance of early introduction of anti-inflammatory therapy in childhood asthma.

Key words: *Asthma – physiopathology; Asthma – blood; Eosinophils – immunology; Asthma – therapy*

Introduction

Asthma is the most common chronic disease in children and adolescents. Over the past decades, asthma has become a prominent healthcare problem in developed countries as it strikes up to 20% of the children population[1-3].

The key pathophysiological process that takes place in the airways of persons suffering from asthma is chronic allergic inflammation involving various proinflammatory cells, i.e. mastocytes, eosinophils, macrophages, platelets and neutrophils as well as respiratory tract epithelial, endothelial and fibroblast cells[4-7]. Cells that predominate the late phase of allergic reaction, the clinical equivalent of which is the asthmatic state, are eosinophils[8-10]. Activated eosinophils release various mediators such as cationic proteins, leukotriene C4 (LTC4) and platelet activating factor (PAF). This leads to the main histopathological processes in asthma, i.e. submucous edema, epithelial damage, and nonspecific bronchial hyper-reactivity (BHR)[11-13].

Eosinophil granulocytes hold around 200 granules, which often contain arginine-rich cationic proteins, i.e. eosinophilic cationic protein (ECP), eosinophil protein X or eosinophil derivative neurotoxin (EPX, EDN), eosinophil peroxidase (EPO), and major basic protein (MB P). ECP, EPX and EPO are located in the granule matrix, and MBP in the granule crystal nuclei. The proteins are released during eosinophil activation[14-18]. ECP is located in the eosinophil granulocyte matrix and makes up to 30% of its content. It is highly cytotoxic for mammals[19].

Research into chronic inflammation of the respiratory tract has led to the introduction of powerful anti-inflammatory medications into asthma treatment. Consequently, it has brought to light the need to objectively evaluate the activity of the allergic inflammatory process[12,20-23]. Clinical symptoms and results of pulmonary function tests do not entirely correspond to the activity of the respiratory tract allergic inflammatory process[23,24].

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Therefore, methods of direct measurement of the inflammatory process activity, such as determining the number and type of inflammatory cells as well as the released mediators in body fluids, have been developed[17,25]. An example of such methods is the immunological assay that ascertains the level of ECP, which is released from activated eosinophil granules, in body fluids[26,27]. Serum ECP level entirely corresponds to the level of ECP in bronchoalveolar lavage, which enables evaluation of the activity of allergic inflammatory process in asthma patients using a significantly less invasive method[27,28].

Patients and Methods

In this study, 100 children aged 6-14 years were followed-up for a 1-year period. All children suffered from allergic (extrinsic) asthma and fulfilled international criteria for prophylactic therapy. Their asthma was either newly diagnosed or they had not received prophylactic therapy for at least 2 months prior to the study onset. Half of the patients were treated with an inhaled corticosteroid, fluticasone propionate (group 1), and the other half with sodium cromoglycate (group 2). Children were randomized using the alternate method: sodium cromoglycate and fluticasone propionate were assigned alternately as patients arrived to the clinic.

Each group was divided into 3 subgroups, depending on the length of the disease prior to the study onset (newly diagnosed, 1-3 years, and >3 years). Group 1, treated with the inhaled corticosteroid, included 19 girls and 31 boys, mean age 8.4 years, age range 6.0-13.5 years. This group was prophylactically treated with inhaled corticosteroid fluticasone propionate in aerosol dispersed by a volumatic device with a mouthpiece or a face mask. The daily dose of fluticasone propionate was divided into two parts administered in the morning and in the evening. Asthma patients whose initial ECP was less than 60 mcg/L received the initial daily dose of fluticasone propionate of 100 mcg/L. Patients whose initial values of ECP exceeded 60 mcg/L were treated with 250 mcg/L of fluticasone propionate. These daily doses of medications were administered for a year.

Group 2, treated with sodium cromoglycate, included 29 boys and 21 girls, mean age 8.8 years, age range 6.0-14.0 years. These patients received sodium cromoglycate as a dry powder packed in gelatinous capsules *via* spinhaler. The daily dose was 4x1 caps a 20 mg (Table 1).

Figure 1 shows the course of asthma in both groups prior to treatment onset. Group 1 included a slightly higher percentage of patients with newly diagnosed asthma (31%) in comparison to group 2 (27%). Both groups included 4% of patients who had suffered from asthma for more than 3 years prior to the beginning of the study.

To evaluate the efficacy of the study, serum ECP (an indicator of allergic inflammation activity) and forced expiratory volume in the first second (FEV1) expressed as % of the expected value, were measured. Serum ECP was measured using radioimmunosorbent eassay (ECP-RIA) according to the manufacturer instructions (Pharmacia Diagnostic AB, Uppsala, Sweden). ECP was first measured before the study and then once a month during the course of the study. ECP-RIA kit measures values within the range of 2-200 mcg/L. The normal value of ECP in healthy person falls in the range of 6-20 ugr/L. The standard spirogram was performed once a month using a Vitalograph spirometer. FEV1 results were expressed as % of the expected value, taking into account sex, age and height of the patient.

The measured values are presented as mean (arithmetic), standard deviation (SD), minimum and maximum. Student's t-test was used to evaluate the difference in ECP and pulmonary function test values between the groups at the beginning of the study and after 12-month treatment. To determine whether there were any significant effects with respect to time and time/group interactions, the groups were tested for all months using "mixed" tests for modeling the covariance structure. The effect of therapy on FEV1 and ECP was analyzed using multiple linear regression. To test ECP and FEV1, we used extended "mixed" model. The p value was set at 0.05 to establish significance.

Results

Prior to the study onset, there was no statistically significant difference in serum ECP (p= 0.0741) be-

Table 1. Patients sex, age and therapy distribution

	Fluticasione propionate	Sodium cromoglycate
No. of patients	50	50
Female	19	21
Male	31	29
Mean age (yrs)	8.4	8,8
Age range (yrs)	6.0-13.5	6.0-14.0

Table 2. Between-group comparison of FEV 1 and ECP at study entry

	Group 1		Group 2	
	Fluticasione propionate		Sodium cromoglycatex	
	χ	STD	χ	STD
FEV 1	71.48	(7.480)	75.24	(8.980)
p	0.0250		0.0251	
ECP µg/L	77.30	(44.130)	665.52	(37.460)
p	0.0741		0.0741	

tween the two patient groups. A statistically significant difference in FEV1 was based on the markedly higher initial values in the group treated with sodium cromoglycate (p=0.0250) (Table 2).

Following 12-month therapy with fluticasone propionate and sodium cromoglycate, a statistically significant between-group difference was recorded in serum ECP (p=0.0031). The group treated with inhaled corticosteroid had a significantly lower ECP. The statistically significant difference in FEV1 (p=0.0000) was caused by significantly higher values in the fluticasone group (Table 3).

Table 3. Between-group comparison of FEV 1 and ECP after 12-months therapy

	Group 1		Group 2	
	Fluticasione propionate		Sodium cromoglycatex	
	χ	STD	χ	STD
FEV 1	94.52	(9.68)	84.18	(11.57)
p	0.0000		0.0001	
ECP µg/L	25.34	(24.08)	41.49	(28.93)
p	0.0031		0.0031	

Figure 2 shows serum ECP in both groups during the study period. In the first three months, a significant decrease in ECP was found in both groups, but it was more pronounced in group 1. By the third month, the values of ECP in both groups were equal. ECP continued to decrease in the group treated with inhaled corticosteroid and reached 23 mcg/L after 10 months of treatment. Its value changed little during the last two months

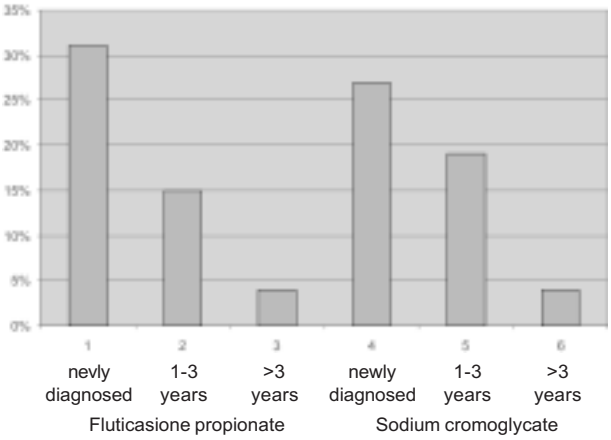

Fig. 1. Disease duration before therapy initiation

of the study (25.3 mcg/L after 12 months). In group 2, treated with sodium cromoglycate, ECP remained at pathological values of 40.0 mcg/L at 9.5 months of treatment and 41.0 mcg/L at the end of the study.

ECP values in the 6 subgroups of patients, 3 of which were treated with fluticasone and 3 with cromoglycate, were related to the duration of asthma before the onset of treatment (Fig. 3). In subgroup 1, the patients with newly diagnosed asthma were treated with fluticasone propionate. Their ECP value before the study was 68 mcg/L. In the first five months, this value decreased significantly to reach the upper limit of the normal range (20 mcg/L). A mild decrease continued for the rest of the study.

Subgroup 2 patients, who had suffered from asthma for 1-3 years before the study, were treated with inhaled corticosteroid. Their initial ECP value was 88 mcg/L, and after 10 months of treatment it decreased to 25 mcg/L.

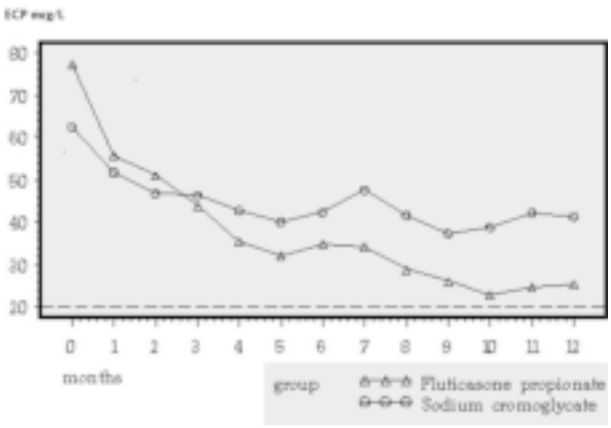

Fig. 2. ECP value during 12 months of therapy

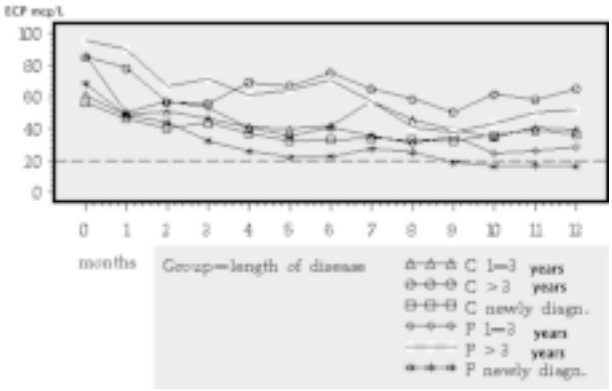

Fig. 3. ECP difference between patient groups according to disease duration

The ECP concentration did not significantly change in the last two months of treatment, so the final result was 29 mcg/L.

Subgroup 3 patients, who had suffered from asthma for more than 3 years before the study, were treated with fluticasone propionate. Their initial ECP value was 96 mcg/L. The lowest level was reached in the 9th month of therapy, however, still exceeding 40 mcg/L. The final measured value was 55 mcg/L.

Subgroup 4 included newly diagnosed patients treated with sodium cromoglycate. This group had the lowest initial ECP results (58 mcg/L), which remained pathological (36 mcg/L) up to the end of the study.

In subgroup 5 patients asthma had lasted for 1-3 years before treatment onset. These patients were treated with sodium cromoglycate. The initial ECP value was 61 mcg/L and decreased to 44 mcg/L at the end of the study.

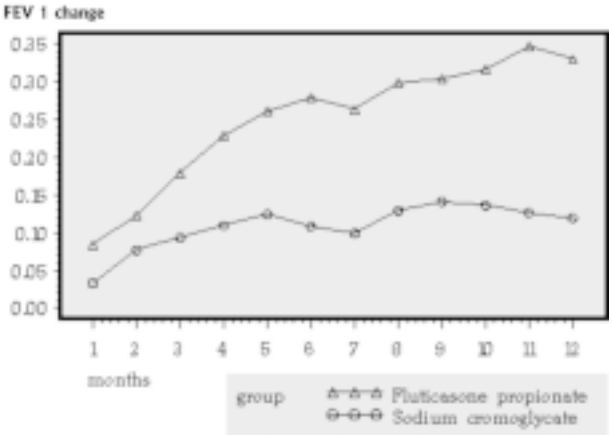

Fig. 4. FEV 1 changes during the study (% of change from initial result)

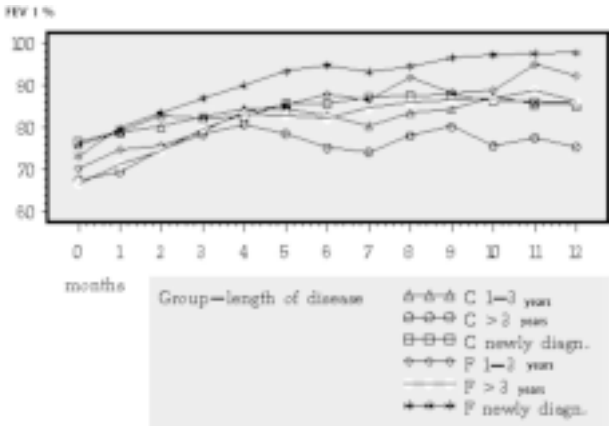

Fig. 5. FEV 1 changes during the study according to patient group (% of expected value)

Subgroup 6 included patients treated with sodium cromoglycate, who had suffered from asthma for more than 3 years prior to the study onset. The initial ECP in this group was 86 mcg/L. No significant decrease was recorded during the course of the study. The final measured value was 70 mcg/L.

FEV1 changes were shown as % of changes from the initial result (Fig. 4). After the first month of therapy, the result was 8% in group 1 and 3% in group 2; at 6 months of therapy, the difference between the groups was 18% (28% in group 1 and 10% in group 2); and at the end of the study, group 1 result was by 21% higher than the result recorded in group 2.

Figure 5 presents FEV1 changes during the study, in relation to the duration of asthma symptoms before the study onset. Patients with newly diagnosed asthma treated with inhaled corticosteroid had the highest FEV1

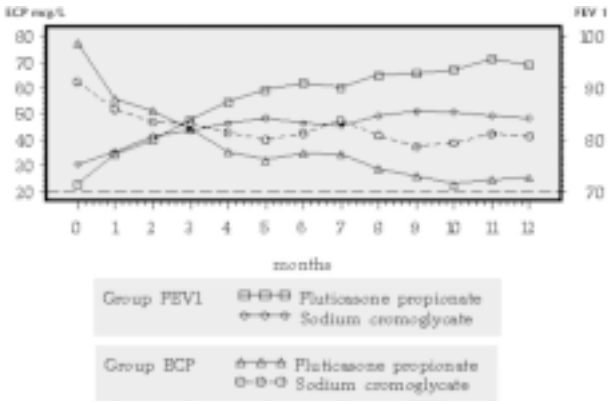

Fig. 6. ECP and FEV 1 changes during 12 months according to patient group

increase, from initial 73% at study onset to 98% of the expected value after 12-month treatment. Patients who had suffered from asthma for more than 3 years and who were treated with sodium cromoglycate showed a non-significant increase of FEV1 from initial 68% to final 75% of the expected value. Comparison between serum ECP and FEV1 during the 12-month treatment is shown in Fig. 6. It clearly demonstrates that the decrease in ECP was followed by an increase in FEV1 in both groups of patients.

Discussion

ECP was measured in all patients before therapy introduction and then once a month during the study to evaluate the efficacy of treatments with inhaled corticosteroid and sodium cromoglycate on allergic inflammation in the respiratory tract mucosa. Previous studies have shown that there is no complete correlation between clinical symptoms and pulmonary function test results on the one hand, and the allergic process activity on the other hand[23,24]. Increased ECP always indicates inflammation, even if it is not strong enough to cause exacerbation of symptoms. Yet, asymptomatic inflammation does require intensive anti-inflammatory therapy[24]. Some studies have, however, pointed to an increased eosinophil and neutrophil chemotactic activity (ECA and NCA) in acute asthma. ECP, on the other hand, is more important as an indicator of chronic inflammatory process that leads to symptomatic exacerbations and irreversible airway changes in asthma patients[19].

Repeat measurements of ECP are much more valuable than one-off measurements to determine fluctuations in the eosinophil activity and in the respiratory tract inflammation[5,23,24]. High eosinophil count in asthma patients is often associated with high eosinophil activity. For asthma patients with normal or slightly increased eosinophil count, it is of much greater importance to assess the eosinophil activity. ECP is an indicator of the activity, and therefore of the inflammatory process itself[5,9,28].

In clinical practice, ECP follow-up may be used to early diagnose the inflammation stage, to follow up therapeutic efficacy, to determine the correct dose of medication and indicate treatment failure as well as to predict acute asthmatic attacks before early symptoms or FEV1[15,26]. The knowledge that the main causes of morbidity and mortality in asthmatic patients are incomplete diagnosis and inadequate therapy increases the importance of ECP measurement. Measuring serum ECP makes possible determining the correct doses of anti-inflammatory medications, that is, the minimal dose that would control the disease. This is particularly important in therapy with inhaled corticosteroids[26].

Chronic inflammation of the respiratory tract in asthma patients may present without clinical symptoms and with normal values of pulmonary function testing. This increases the risk of the development of asthma symptoms, attacks and exacerbations[19,24]. Pathological values of ECP may indicate asymptomatic chronic inflammation with normal pulmonary function, and consequently justify the introduction of anti-inflammatory treatment[24,30].

The results of the present study showed that during the 12-month period the values of ECP decreased in both patient groups. There was, however, a statistically significant difference between the two groups. At the end of the study, the mean value of ECP in the group treated with fluticasone propionate was 25.35 mcg/L, and in the group treated with sodium cromoglycate 41.49 mcg/L. Therefore, the asthma patients treated with inhaled corticosteroid had ECP values at upper limits of the normal range, and those treated with sodium cromoglycate above 40 mcg/L. According to some studies, the latter values signify a risk of chronic persistent asthma.

These findings support previous studies that compared inhaled corticosteroids with cromons, in which inhaled corticosteroids were shown to be more effective in improving pulmonary functions and reducing clinical symptoms, together with a significant decrease in ECP[21,32,33].

This study demonstrated a significant positive correlation between the decrease (normalization) of ECP values and duration of asthma symptoms before the introduction of anti-inflammatory therapy. The fact that ECP normalization depends on the duration of asthma prior to therapy initiation points to the importance of early introduction of prophylactic therapy with inhaled corticosteroid. The early introduction of prophylaxis should quickly normalize ECP, and consequently prevent further progress of chronic respiratory tract inflammation and irreversible changes.

Conclusion

The study following up 100 children over a 12-month period showed that the fastest decrease in ECP and highest FEV1 values were recorded in children with newly

diagnosed asthma treated with inhaled corticosteroids for 12 months. These results demonstrate that early introduction of inhaled corticosteroid in the treatment of childhood asthma brings about quick suppression of allergic inflammation in the airways and normalization of ECP (an as indicator of asthma activity in the airways), thus preventing permanent changes in the respiratory tract.

Asthma is a widespread chronic disease. Its subjective and economic aspects require development of objective methods for assessment of the disease activity, treatment efficacy, and, if possible, prevention of attacks. Measurements of ECP should serve as an objective indicator of allergic inflammation activity.

We followed 100 children aged 6-14 years suffering from asthma with persistent symptoms. The introduction of anti-inflammatory treatment was therefore fully justified. One half of the patients were treated with an inhaled corticosteroid (fluticasone propionate), and the other half with sodium cromoglycate. To evaluate the efficacy of the treatment, the values of serum ECP and FEV1 were measured before the beginning of the study and then once a month for a year.

The fastest drop in ECP values (whereby ECP was used as an indicator of the allergic inflammatory process activity in the respiratory tract) and the highest increase in FEV1 were found in children with newly diagnosed asthma, who were treated with inhaled corticosteroid. These results support the importance of early introduction of anti-inflammatory therapy in childhood asthma. This therapy suppresses the allergic inflammation in the airways, and ECP is an indicator of the allergic inflammation activity. By suppressing the allergic inflammation in the airways, irreversible changes such as respiratory tract remodeling, are prevented.

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Sažetak

ASTMA I EOZINOFILNI KATIONSKI PROTEIN KAO POKAZATELJ USPJEŠNOSTI LIJEČENJA BOLESTI

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Astma je najčešća kronična bolest djece i mladeži. Zahtijeva razvoj objektivnog mjerila kojim će se moći pratiti aktivnost bolesti, učinkovitost primijenjene terapije te eventualno predvidjeti napadaji. Mjerenje eozinofilnog kationskog proteina (ECP) ima upravo vrijednost jednog takvog objektivnog parametra aktivnosti alergijske upale. Tijekom 12 mjeseci pratili smo stotinu djece s astmom koji su u terapiji dobivali inhalacijski kortikosteroid (flutikazon propionat) ili natrijev kromoglikat. Kao pokazatelj učinkovitosti primijenjene terapije kod bolesnika se je pratila vrijednost serumskog ECP i forsiranog ekspiracijskog volumena (FEV1) u 1 sekundi prije početka ispitivanja te jedanput na mjesec tijekom 12 mjeseci. Najbrži pad ECP uz najviši porast FEV1 zabilježen je u skupini djece s novootkrivenom astmom na terapiji inhalacijskim kortikosteroidom. Ovo ukazuje na značenje ranog uvođenja protuupalne terapije u liječenju dječje astme.

Ključne riječi: *Astma – fiziopatologija; Astma – krv; Eozinofili – imunologija; Astma – terapija*