

Eosinophil cationic protein and myeloperoxidase in nasal secretion as markers of inflammation in allergic rhinitis

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The inflammatory component of allergic rhinitis was studied by measuring the concentration and content of eosinophil cationic protein (ECP, specific for eosinophils) and myeloperoxidase (MPO, specific for neutrophils) in samples of nasal secretion from 20 pollen-allergic subjects. All secretion samples contained measurable concentrations of both proteins. The mean ECP concentrations on two occasions without pollen exposure were 950 and 1170 $\mu\text{g/l}$. The ECP concentration during the pollen season without any therapy (mean 1160 $\mu\text{g/l}$) did not differ significantly from the baseline values, but intranasal corticosteroid therapy resulted in a significant decrease (mean 530 $\mu\text{g/l}$). The concentration of MPO was about 10 times higher than that of ECP, but the changes in MPO were nonsignificant throughout the observation period. An inverse correlation was found between the threshold dose in histamine challenges and the ECP level expressed either as concentration or as content. Furthermore, the ECP concentration and content 1 day after a positive allergen challenge were both significantly correlated with the strength of the challenge reaction. Measurements of ECP in nasal secretions are useful for studying the presence and activity of eosinophils in the nasal mucosa, and may prove of value in clinical investigations on patients with allergic rhinitis.

Key words: corticosteroids; eosinophils; hypersensitivity; nasal secretion; nasal provocation test.

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CLINICAL ASPECTS

The activity of inflammatory effector cells in the nasal mucosa may be important for the clinical manifestations of allergic rhinitis. The observations that the ECP level on the day following allergen challenge is correlated with the strength and duration of the challenge reaction, and also that the histamine reactivity is correlated with the ECP level, support this view.

Allergic rhinitis is an inflammatory condition of the nasal mucous membrane, triggered by immunological events. The traditional Coombs-Gell type I reaction adequately describes the trigger, whereas the clinical manifestations seem to be more closely related to the inflammatory component of the reaction.

In allergic asthma, a link has been established between inflammation in the airway, hyperreactivity to non-allergic irritants and a tendency to display a dual response to allergen

challenge (1, 3, 8, 9, 11). Especially interesting evidence of the importance of inflammation in the late bronchial response has been presented by de Monchy et al. (14). They performed repeated bronchial lavages in patients after allergen challenges and observed that when the patients experienced a late reaction to challenge, the level of eosinophil cationic protein (ECP), a granule specific protein of the eosinophil (21), was increased. This increase was found only at the time of the reaction and did

not occur in patients who only exhibited an early response.

Little is known about the inflammatory component of allergic rhinitis and its possible link with a dual response. The aim of the present study was to estimate the degree of inflammation in this condition by biochemical means and also to assess its possible relationship with allergy symptoms. The participation of eosinophils in the inflammation was assessed by measurements of ECP. The neutrophil involvement was studied by measurements of myeloperoxidase (MPO), a protein specific for primary granules of neutrophils (16, 22).

MATERIAL AND METHODS

Study design

It was planned that each patient should provide a nasal secretion sample at each of five visits. A flow chart showing the design of the study is presented in Fig. 1. The aim of the studies at visits 1–3 was to investigate any changes in the granulocyte proteins during natural exposure to pollen and intranasal corticosteroid therapy compared with the off-season baseline values. Starting after visit 1, the patients were treated with beclomethasone dipropionate 200 µg bid, (Becotide Nasal®, Glaxo), abbreviated BDP. The sampling during therapy was scheduled to take place at least 1 week after this therapy had begun. It was considered that this interval would be long enough for a clinical effect to become manifest but short enough for the last patients to return before the end of the birch pollen season. At visits 4 and 5 the aim was to reproduce allergic symptoms by means of nasal allergen challenge out of season, and to determine whether they were accompanied by changes in the granulocyte proteins. The fourth sampling was immediately followed by a birch pollen challenge and the fifth was scheduled to take place 1 day after that challenge.

The allergic condition of the patients was further characterized by three measures, subjective ratings, nasal reactivity to histamine,

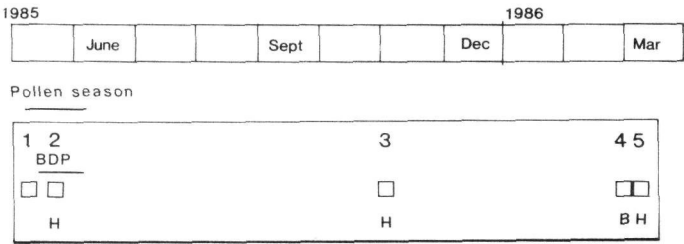


Fig. 1. The design of the study. Squares indicate sampling of nasal secretion, one sample being obtained at each visit. Challenges are marked H for histamine and B for birch pollen. The nasal secretion sampling always preceded the challenge. The bar marked BDP indicates topical beclomethasone dipropionate therapy.

and volume of nasal secretion sampled, for correlation with the ECP and MPO values. Subjective ratings were recorded, using both an overall visual analogue scale (VAS) (19) and a summed symptom score. For the symptom score, the patient was asked to rate each of the symptoms nasal congestion, sneezing and rhinorrhea as absent, slight, moderate or severe. Provoked as well as naturally occurring symptoms were assessed. The nasal reactivity to histamine was tested at the second, third and fifth visit. During the season, some patients did not improve enough to allow determinations of the effect of exogenous histamine, and were therefore not challenged. Finally the volume of nasal secretion obtained in each sample was measured.

When a challenge was performed, whether histamine or allergen, the nasal secretion sample obtained at that visit was always taken before the challenge.

Patients

The patients were recruited during the birch pollen season of 1985. All patients in whom a tentative diagnosis of allergy was established, and in whom none of the exclusion criteria applied, were asked to participate in the study. The final decision to include the patient in the analysis was made after the birch pollen allergy had been demonstrated by nasal challenge later in the study.

Exclusion criteria were the coexistence of a

nonallergic nasal disease, chronic disease other than atopic allergy, pregnancy, immunotherapy for allergy during the last 3 years, age over 50, or refused consent. The patients were not on any therapy when they entered the study. Those who rejected continuous therapy or were otherwise unsuitable for intranasal corticosteroid treatment were excluded. Patients with asthma were excluded from nasal challenges. Episodes of bronchospasm during the birch pollen season were regarded as a criterion for exclusion only if they were so severe or protracted that the patient required therapy.

Forty-three patients were screened for the study. Twenty patients, with a confirmed diagnosis of birch pollen allergy, remained at visit 3 and were included in the analysis of the first part of the study. Five of these patients were men and 15 women. Their mean age was 27 years (range 18–43 years). One of these 20 patients did not attend visit 2. Birch pollen challenges was carried out on 15 of the patients. Eleven of the patients were considered allergic to other pollens and seven to other allergens as well, mainly cat. No patients had allergic symptoms when seen out of season. During the season, topical treatment for conjunctivitis was allowed, and three patients reported occasional use of antihistamine tablets, but not on histamine challenge days.

Informed consent was obtained before any patient was included in the study. The study design was approved by the Ethics Committee of the Medical Faculty of the University of Uppsala.

Sampling of nasal secretion

Samples of nasal secretion were collected by means of nasal spray washing (10). Lithium chloride was added to the washing solution as an exogenous marker so that the volume of secretion in the sample could be calculated and the concentrations observed could be corrected for the dilution incurred by the washing (12). The lithium concentration of the washing fluid was increased, from approximately 1

mM in the original method, to approximately 2 mM in order to increase the accuracy when samples with low secretion contents were analyzed. The two nasal cavities were sprayed repeatedly with 0.9% sodium chloride, and after 200–300 μ l had been introduced, the patient expelled the fluid into a plastic dish. The collected fluid was transferred to a preweighed plastic tube. It was then filtered through a 5 μ m Millipore filter, and the filtrate was frozen to -20°C pending assay. Calculated secretion contents down to 3% were considered reliable. Values below that level were rounded to 3% in order to reduce the risk of overestimating the concentrations of the granulocyte proteins. This applied to 3, 5, 5, 5, and 5 samples at the five visits, in that order. It also affects the calculation of secretion volumes, but not the calculation of the absolute contents of granulocyte proteins.

Determination of granulocyte proteins

ECP was measured by a radio-immunoassay procedure as described by Venge et al. (21) and MPO by a similar procedure (16). Some samples were too small to allow both proteins to be assayed, and in those cases only ECP was measured. The analysis of one sample at each of visits 1 and 5 failed. The numbers of samples analyzed for ECP and MPO at each visit are shown in Fig. 2.

Nasal challenges

The criteria for positive allergen and histamine challenges were based on the subjective response. After each dose the patients counted the number of sneezes and rated rhinorrhea and nasal congestion on a four-level scale as absent, slight, moderate, or severe, as described by Pipkorn (18). A minimum positive response to the challenge was defined as one symptom rating as moderate or two symptoms rating as slight. This protocol has been used in a previous study by Linder et al. (13).

Intranasal histamine challenges were carried out with histamine hydrochloride in 0.9% sodium chloride solution. Each time, 300 μ l

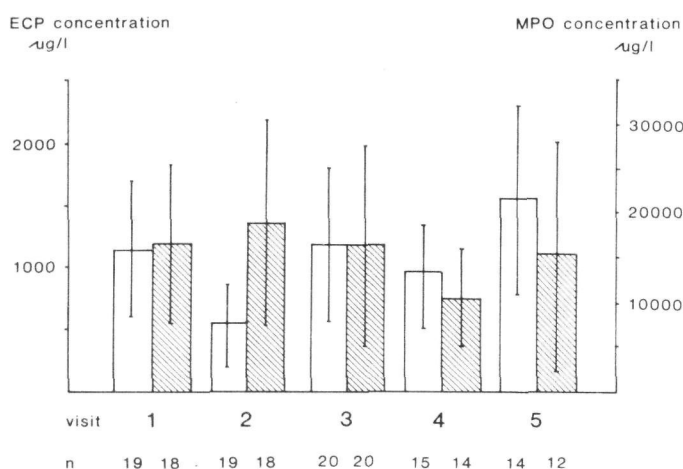


Fig. 2. The mean concentrations of eosinophil cationic protein (ECP; open bars, left-hand scale) and myeloperoxidase (MPO; filled bars, right-hand scale) in the nasal secretion samples. The 95% confidence intervals are indicated for each mean. "n" stands for the number of analyzed samples.

was instilled into one nostril. The challenge was begun with a dose equivalent to 12.5 µg of histamine base. The dose was progressively doubled, and the test was carried on until a positive reaction was provoked or a dose of 400 µg had been given. No diluent blank was included, since the challenge was preceded by washing with 0.9% sodium chloride for sampling purposes. One patient did not consent to histamine challenge at visit 3 and another patient had to be excluded from the histamine challenge at visit 5 for lack of time.

The allergen challenges were carried out with birch pollen extract in albumin diluent (Spectralgen®, Pharmacia). The test was begun with a diluent blank and continued through 100, 1000, 10,000, and 100,000 biological units (BU) or discontinued when a positive reaction was provoked. Allergen challenges were carried out in one nasal cavity, and care was taken to see that the subsequent histamine challenge was applied to the same side.

Statistical analysis

Significant testing of changes in a variable between two measurements were carried out by means of Wilcoxon's matched pair test.

Correlations were evaluated with Spearman's rank correlation coefficient (r_s).

RESULTS

Eosinophil cationic protein

All samples contained measurable quantities of ECP. The mean ECP concentration in the samples (Fig. 2) was significantly lower ($P < 0.05$) at visit 2, when the patients had been treated for 1 week with BDP during the season (530 µg/l, SD 660), than at visit 1, before treatment (1160 µg/l, SD 1140). The mean concentration at visit 3, after the season (1170 µg/l, SD 1330), was significantly higher than at visit 2 ($P < 0.05$), but did not differ significantly from the value at visit 1.

The mean total ECP content in the nasal secretion samples showed the same pattern. There was a significant difference ($P < 0.05$) between the value obtained at visit 2, during therapy, (70 ng/sample, SD 60) and visit 1, before therapy, (180 ng/sample, SD 240). The value at visit 3 (130 ng/sample, SD 140) also differed significantly from that at visit 2 ($P < 0.05$), but the difference between the ECP content at visits 1 and 3 was not significant.

As shown in Fig. 2, the mean ECP concentration was higher at visit 5, after birch pollen challenge (1550 µg/l, SD 1330), than at visit 4 before challenge (950 µg/l, SD 720), but this difference was not significant. The mean ECP content was 90 ng/sample (SD 60) pre-challenge and 170 ng/sample (SD 190) post-challenge, a nonsignificant difference. Six out of 15 challenged subjects reported that their symptoms persisted on the day after the challenge, but none experienced a dual response. The subgroup with persistent symptoms was found to have a significantly ($P < 0.02$) higher ECP content postchallenge (visit 5) than the subgroup free from symptoms.

Myeloperoxidase

All samples assayed for MPO contained measurable quantities of that protein. The mean

MPO concentration in nasal secretion at the five visits is illustrated in Fig. 2. The differences were nonsignificant. Nor did the mean MPO content, which ranged between 1060 (SD 1010) and 2900 ng/sample (SD 4600), change significantly during the study period.

There was a significant positive correlation between the MPO and ECP concentrations, except at the first visit (see Table). To make sure that the round-off error in samples containing less than 3 % secretion did not lead to false conclusions about the significance of observed differences in concentrations of granulocyte proteins, statistical tests were also performed after exclusion of those samples. The results were unchanged.

Subjective ratings

The correlations between the subjective ratings, both VAS and summed symptom score, and the ECP values during the season – at visits 1 and 2 – did not reach the level of significance. There was a significant correlation, however, ($r_s = 0.74$, $P < 0.01$) between the subjective VAS rating of the birch pollen challenge reaction (visit 4) and the ECP concentration at visit 5 on the next day (Fig. 3). Similar correlations were found between the ECP content and the subjective ratings mentioned above.

The MPO values did not correlate with the subjective ratings at any visit.

Histamine reactivity

The histamine reactivity is illustrated in Fig. 4. It was highest on the day after the birch pollen

Table 1

Correlation between the concentrations of eosinophil cationic protein and myeloperoxidase in samples of nasal secretion

Visit	1	2	3	4	5
<i>n</i>	18	18	20	14	12
<i>r_s</i>	0.37	0.69	0.92	0.93	0.85
<i>P</i>	NS	< 0.01	< 0.002	< 0.002	< 0.01

n = number of samples analyzed for both ECP and MPO.
r_s = Spearman's rank correlation coefficient.

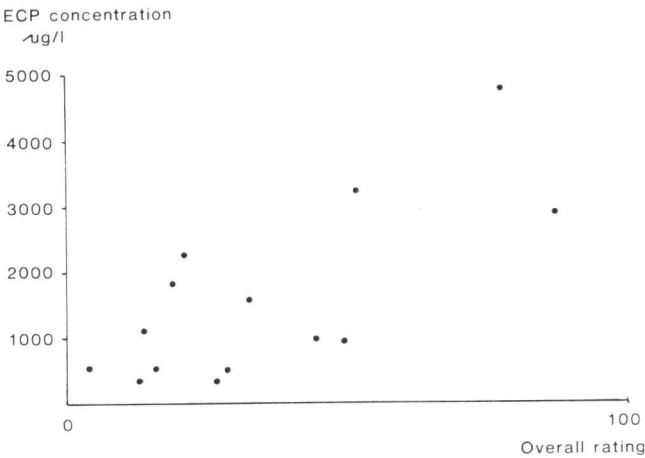


Fig. 3. The correlation between the overall rating of the reaction provoked by the birch pollen challenge (visit 4), and the concentration of eosinophil cationic protein in nasal secretion on the following day (visit 5).

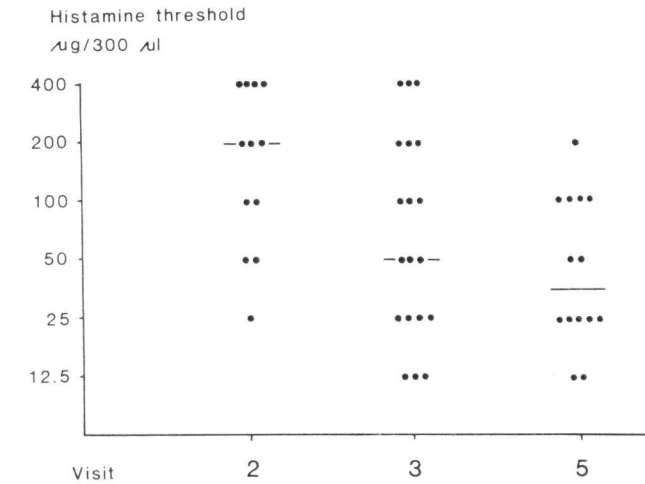


Fig. 4. The nasal histamine threshold (dose required to provoke a reaction) during corticosteroid treatment in the pollen season (visit 2), under baseline conditions postseason (visit 3) and 1 day after nasal birch pollen challenge (visit 5). Bars indicate medians.

challenge (visit 5) and lowest during BDP treatment in the season (visit 2). The difference in reactivity between these two occasions was statistically significant ($P < 0.05$). It should be noted that the histamine reactivity could not be assessed in seven patients at visit 2, during treatment for seasonal allergy, because of the presence of symptoms which were greater than or equal to the minimum response required as a criterion of a positive challenge. The histamine reactivity at visit 5, one day after a positive allergen chal-

lenge, was significantly ($P < 0.05$) higher than the baseline value at visit 3.

A negative correlation was found between the histamine threshold and the ECP concentration ($r_s = -0.36$, $P < 0.02$), and between the histamine threshold and the ECP content ($r_s = -0.31$, $P < 0.05$), calculated from 44 histamine challenges. (The ECP assay of one sample failed.) The correlation between the histamine threshold and the ECP values was also calculated separately for each of visits 2, 3, and 5. Negative but nonsignificant r_s values were found (between -0.15 and -0.34).

No correlation were noted between the histamine reactivity and the MPO values.

Secretion volume

The mean secretion volume was somewhat larger at visit 1 (210 μ l, SD 210) than at visits 2 through 5, (130–180 μ l, SD 130–180). The differences were not significant.

There was a significant correlation between the secretion volume and the ECP content at visit 1 ($r_s = 0.50$, $P < 0.05$). The correlation between these two variables at visits 2, 3, 4, and 5 did not reach the level of significance, $r_s = 0.42$, 0.16 , 0.21 , and 0.40 respectively.

An inverse relationship was found between the secretion volume and the concentrations of ECP at visit 2 ($r_s = -0.48$, $P < 0.05$) and visit 3 ($r_s = -0.65$, $P < 0.01$) and MPO at visit 3 ($r_s = -0.58$, $P < 0.01$), but otherwise no correlations were found between this volume and the concentrations of the granulocyte proteins.

There was a significant ($P < 0.05$) positive correlation ($r_s = 0.50$) between the secretion volume and the MPO content at visit 1 but there was no correlation at the other four visits.

DISCUSSION

Inflammation is being increasingly recognized as a major factor in allergies of the respiratory tract. Two phenomena that are possibly related to the inflammatory mechanisms are nasal priming and late phase reactions.

The term “priming of the end organ” was

coined by Connell in 1968 (4) to describe an increased nasal reactivity to allergens, induced by natural allergen exposure or by an allergen challenge. The induced nasal hyperreactivity also extends to cholinergic stimuli (7) and histamine (2, 15).

Taylor & Shivalkar (20) first described a late nasal reaction following allergen challenge in 1971. The prevalence of clearcut dual reactions to nasal challenges has been debated, and figures ranging from 50% (6) to fewer than 10% (17) of the tested patients have been reported.

The role of eosinophils in bronchial challenge reactions has been studied by de Monchy et al. (14). They performed repeated bronchial lavages in patients undergoing bronchial challenge, and found that the human bronchial late-phase reaction is characterized by a rise in the ECP concentration in the lavage fluid, indicating an infiltration of eosinophils into the mucosa. The ECP concentration did not rise in negative challenges or isolated early reactions. Blood eosinophil counts in bronchial challenges (5) also point to an association between the bronchial late-phase reaction and eosinophil activation.

The histamine concentration and content in nasal secretion of patients with allergic rhinitis have been found to decrease in reproducible fashion on development of symptoms of allergy (13). It is possible that these changes do not adequately reflect the pathophysiological events underlying the symptoms. The release of mast cell mediators is a rapid process, while the inflammatory reaction takes hours to develop or subside. Indices of inflammation may therefore be expected to be more stable than indices of mast cell degranulation.

This is the first study of eosinophil cationic protein and myeloperoxidase in nasal secretions. In the following discussion, “ECP level” and “MPO level” will be used as comprehensive terms for the concentration and content of the respective granulocyte proteins, since these two measures showed parallel changes in each protein. The levels chiefly represent free granulocyte proteins, since the samples were filtered before analysis. The ECP concentrations observed in the present study are high compared

with the reference concentration in serum in healthy individuals, 5–55 $\mu\text{g/l}$ (21). The same applies to the MPO concentrations in relation to the reference value of 121 $\mu\text{g/l}$ (geometric mean) for MPO in serum (22). The levels in nasal secretions thus measure locally liberated proteins rather than spill-over from the circulation. The ECP level showed significant fluctuations, while the MPO level remained steady during the investigation.

The main issue of the present study was whether there is a relationship between granulocyte protein levels in nasal secretions and the degree of severity of allergic rhinitis. Changes in the severity of the allergic disease were produced by natural exposure to pollen and by pollen challenge. No attempt was made to maximize the changes. The challenges were only carried to a threshold dose, and the sample during the pollen season was taken at the first visit, even through some patients had only weak symptoms on that occasion. With this strategy, there is a risk that some of the responses will not be sufficient and will therefore distort the results for the group.

There is no measure which can serve as a calibration standard. The changes in the allergic condition were assessed on the basis of subjective ratings, determinations of the nasal histamine reactivity and measurements of the volume of nasal secretion obtained in each sample.

The relationship between the level of ECP and the allergic condition in the nose was demonstrated by the positive correlation between the subjective rating of the birch pollen challenge reactions and the ECP level on the following day. The average increase in the ECP level following the allergen challenge did not reach significance, a fact which probably implied that the predefined minimum clinical response was inadequate. The small mean change in the secretion volume supports this.

A correlation between the ECP level and the histamine reactivity was also observed. The increase in histamine reactivity after allergen challenge is an example of nasal priming. This indicates that the ECP values have pathophysiological significance. Another indi-

cator of this is the observed association between an increased content of ECP post-challenge and persistent nasal symptoms. This observation fits well with the findings in bronchial challenges discussed above (14), although the clinical manifestations after the nasal challenges were described by the patients as one prolonged reaction rather than a dual response.

The volume of the recovered secretion is mathematically related to the concentration and content of the granulocyte proteins. This complicates the interpretation of correlations between the volume and the granulocyte protein levels. The correlation between the ECP content and the volume is compatible with the conclusion that allergic symptoms are associated with elevated levels of ECP.

The interpretation of the data from the pollen season deserves some consideration. When entering the study, most patients were symptomatic although the symptoms were by no means maximal. Treatment with BDP brought about a subjective improvement in the majority of cases. At the two baseline visits outside the pollen season, no patient had symptoms. The ECP level indicated the change during corticosteroid therapy but not the difference between the first seasonal visit and those outside the season. There is no reason to believe that the patients suffered from active allergic rhinitis during the off-season visits. Thus the first season values are lower than might be expected, and this may reflect that the patients do not wait for a full-blown rhinitis before seeking help. On the other hand, the ECP level was remarkably sensitive to topical treatment with BDP. This observation brings up the possibility that the response of the eosinophil granulocytes to corticosteroids exceeds that of the clinical condition. It is known that the eosinophil granulocyte is more sensitive to corticosteroids than the neutrophil, which explains why MPO did not decrease significantly at the same time.

We conclude that it is possible to detect changes in the concentration and content of ECP in nasal secretion during different phases of pollen allergy, and that these changes are linked to the clinical course of the disease. The

latter was not found for MPO. Measurements of ECP are useful for studying the presence and activity of eosinophils in the nasal mucosa, and may prove of value in clinical investigations on patients with allergic rhinitis.

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