

## Comparative clinical and airway inflammatory features of asthmatics with or without polyps\*

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### SUMMARY

**Background:** Nasal polyposis (NP) is associated with a more severe and steroid-resistant asthma.

**Objective:** To compare clinical and airway inflammatory features of asthmatics with or without NP.

**Methods:** Two groups of asthmatic patients were studied: group 1 with NP and group 2 without NP. Asthma control was assessed according to the Asthma Control Scoring System (ACSS). Expiratory flows, induced sputum, and blood eosinophils were also measured.

**Results:** The ACSS score was lower (poorer control) in group 1 compared with group 2. FEV<sub>1</sub> and the FEV<sub>1</sub>/FVC ratio was lower in group 1 compared with group 2. Blood and induced sputum eosinophils, as well as fibronectin and eosinophil cationic protein levels were higher in group 1.

**Conclusion:** Asthmatic subjects with NP have increased airway obstruction, more inflammatory cells and reduced asthma control compared to those without NP. This may suggest a contribution of nasal polyps to the severity of asthma or a common susceptibility to develop upper and lower airways mucosal inflammation.

*Key words:* asthma, induced sputum, nasal polyposis, eosinophil, asthma control

### INTRODUCTION

Nasal polyposis is a chronic inflammatory disease of the upper airways affecting about 5% of asthmatic patients<sup>(1,2)</sup>. The prevalence of polyposis and sinus disease is even higher in subjects with severe asthma<sup>(2,3)</sup>. The concept of "united airways" has emerged mainly from studies on allergic rhinitis and asthma<sup>(4)</sup>, but other upper airway diseases, such as chronic rhinosinusitis and nasal polyposis may influence lower airway conditions. Severe chronic sinus disease is considered a risk factor for frequent asthma exacerbations<sup>(5)</sup> and medical or surgical treatment of chronic rhinosinusitis can improve asthma control in the majority of patients<sup>(6,7)</sup>.

Eosinophils often constitute more than 60% of the nasal polyps cell population, but activated mast and T cells are also found<sup>(8)</sup>. Previous studies demonstrated that eosinophil counts within nasal and bronchial mucosa were higher in subjects with nasal polyposis and associated asthma or airway hyperresponsiveness compared to those with isolated nasal polyposis<sup>(9-11)</sup>. Moreover, ten Brinke et al. showed that sputum eosinophils are increased in severe asthmatic subjects with extensive chronic rhinosinusitis compared to control subjects with limit-

ed sinus disease<sup>(12)</sup>. An increased production of cytokines, growth and chemotactic factors, such as granulocyte macrophage colony stimulating factor (GM-CSF), interleukin (IL)-5, RANTES (CCL5) and eotaxin (CCL11) seem to be associated with this pathology and may contribute to the severity of asthma<sup>(13-15)</sup>. However, there is a need for studies comparing clinical and inflammatory features of nasal polyposis subjects with different asthma severities.

The aim of this study was to determine if the presence of nasal polyps in asthmatic patients was associated with a poorer asthma control, increased airway obstruction and more marked inflammatory profile.

### MATERIALS AND METHODS

#### Subjects

A total of 79 asthmatic subjects, aged between 18 and 60 years, were included in the study. Two types of subjects were recruited: with a proven nasal polyposis (group 1) and without nasal polyposis (group 2). Aspirin sensitivity was not an exclusion criterion, and specific history was not investigated. All subjects were non smokers and were recruited from the Laval Hospital

Asthma Clinic and ENT Clinic. All subjects signed an informed consent form and the protocol was reviewed and approved by the Institutional Ethics Committee.

#### Definitions

Nasal polyposis was confirmed by the identification of nasal polyps on clinical examination. When available, results from sinus CT scan, done within the last two years, were also recorded. Asthma was defined according to the criteria of the American Thoracic Society (ATS) <sup>(16)</sup>. The severity and control of asthma were determined according to the Canadian Asthma Consensus Guidelines <sup>(17)</sup>. Atopy was defined as at least one positive skin test response to a battery of common airborne allergens.

#### Study design

All patients came to the laboratory for an evaluation of asthma control according to the recently developed and validated Asthma Control Scoring System (ACSS), a physical examination with a particular attention to the presence of nasal polyps, a skin prick test with a battery of common allergens, a spirometry with measurement of expiratory flows, a blood sampling for complete blood count, and an induced sputum with differential cell count.

#### Asthma Control Scoring System questionnaire (ACSS)

An interviewer administered this questionnaire. Three types of parameters: clinical, airflow limitation, and lower airway inflammation were obtained. The different parameters are quantified to obtain a total score of 100% each and a global score is determined using the means of these parameters <sup>(18,19)</sup>.

#### Skin prick tests

Atopy was determined from skin prick tests done with 26 common aeroallergens (including animal dander, tree and grass pollens, molds, and house dust mites). Normal saline and histamine were used as negative and positive controls, respectively. Skin wheal diameter was recorded at 10 min as the mean of 2 perpendicular measurements. A positive response was defined as a skin wheal diameter of 3 mm or more.

#### Spirometry

Prior to spirometry, short acting  $\beta_2$ -agonists and long acting  $\beta_2$ -agonists were withheld for 8 h and 12 h, respectively. Subjects also refrain to take leukotriene antagonists for 24 h before the tests. Inhaled and nasal corticosteroids were not stopped prior to the tests.

Baseline forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) were measured according to the ATS criteria <sup>(20)</sup> using a Medisoft micro 5000 spirometer (Roxon, Montreal, QC, Canada). The predicted values were obtained from Knudson <sup>(21)</sup> and FEV<sub>1</sub> was defined as the best of 3 reproducible values.

#### Induced sputum

Sputum was induced by inhalation of hypertonic saline using the method described by Pin et al. <sup>(22)</sup> and modified by Pizzichini et al. <sup>(23)</sup>. Sputum was processed within 2 h following induction. Briefly, mucus plugs were selected from saliva, weighed, treated with 4 times their volume of dithiothreitol (DTT; Sputolysin; Calbiochem Corp., La Jolla, CA, USA) and rocked for 15 min. An equal volume of Dulbecco's phosphate buffered saline 1X (D-PBS; Life Technologies (Gibco BRL), Burlington, ON, Canada) was then added, and the solution was filtered and counted to determine total cell count and viability. Two slides were prepared and stained with Diff-Quik (Dade Diagnostics of P.R. Inc., Aguada, PR, USA) for differential cell count. Fibronectin was measured in sputum supernatant by EIA (Takara Bio USA, Madison, WI, USA). Eosinophil cationic protein (ECP, MBL International, Boston, MA, USA), vascular endothelial growth factor (VEGF, R&D Systems, Minneapolis, MN, USA), matrix metalloproteinase (MMP)-9 (R&D Systems), tissue inhibitor of metalloproteinase (TIMP)-1 (R&D Systems) were measured in supernatant by ELISA according to the manufacturer's instructions.

#### Blood sampling

Complete blood count was performed on blood samples.

#### Statistical analyses

Statistical analyses were done by an experienced biostatistician. Gender and atopy were analysed using the Chi-Square test. Results of representative measures were expressed as mean  $\pm$  SD or as mean  $\pm$  SEM, for continuous variables, as appropriate. Student's t-test was performed to compare between group 1 and group 2. All cell count variables were analysed with a log-transformation to stabilize variance. Expiratory flows and ACSS scores were analysed using the  $\sin^{-1}(\sqrt{\cdot})$  transformation. Statistical results from these parameters were expressed with transformed values. A one-way ANOVA was performed to analyse the data according to medication use. The univariate normality assumption was verified, as well as graphical representations of the Shapiro-Wilk test. The Brown and Forsythe's variation of Levene's statistic test was used to verify the homogeneity of variances. The results were declared significant with p-values < 0.05. The data were analysed using the statistical package program SAS v9.1.3 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

#### Subjects' characteristics

Seventy-nine subjects participated in the study. Their characteristics are shown in Table 1. Subjects were significantly older in group 1 compared with group 2 (p < 0.0001). Twenty-four subjects from group 1 and 20 from group 2 were using inhaled corticosteroids (ICS) for asthma; the mean daily dose of ICS was significantly higher in group 1 (p = 0.04).

Table 1. Subjects' characteristics.

Group	1	2
n	39	40
Age (y) *	45 ± 12 <sup>§</sup>	30 ± 9
Gender (F/M)	21/18	26/14
Atopy (+/-)	27/12 <sup>§</sup>	40/0
Inhaled Beclomethasone or equivalent* (µg) <sup>‡</sup>	391 ± 202 <sup>  </sup>	266 ± 168
Nasal Mometasone or equivalent* (µg) <sup>‡</sup>	277 ± 139	—
FEV <sub>1</sub> (% pred.) <sup>†</sup>	81 ± 3 <sup>  </sup>	96 ± 3
FEV <sub>1</sub> /FVC <sup>†</sup>	70 ± 2 <sup>  </sup>	76 ± 1
ACSS Score <sup>†</sup>		
Clinical	89 ± 2	90 ± 2
Physiological	78 ± 4 <sup>  </sup>	90 ± 3
Inflammatory	54 ± 5	67 ± 4
Global	73 ± 3 <sup>  </sup>	82 ± 2

Results are presented as means ± SD\* and as means ± SEM<sup>†</sup>. <sup>‡</sup> When applicable. <sup>§</sup>p < 0.0001. <sup>||</sup> p < 0.05. FEV<sub>1</sub>: forced expiratory volume in one second, FVC: forced vital capacity, ACSS: asthma control scoring system.

Table 2. Blood and sputum inflammatory parameters.

Group	1	2
Sputum		
Eosinophil %	11.1 ± 2.6*	3.9 ± 0.9
Eosinophil count/g mucus (x10 <sup>6</sup> cells/g)	0.7 ± 0.2 <sup>†</sup>	0.15 ± 0.06
Levels of fibronectin (ng/ml)	309 ± 62*	138 ± 23
Levels of ECP (ng/ml)	486 ± 115*	208 ± 60
Blood		
Eosinophil (%)	5.5 ± 0.6*	3.9 ± 0.4
Absolute eosinophil count (x10 <sup>6</sup> cells)	0.4 ± 0.05*	0.3 ± 0.03

Results are presented as means ± SEM. \* p < 0.05. <sup>†</sup> p < 0.01. ECP: eosinophil cationic protein

#### Asthma control

The results of the ACSS score are shown in Table 1. Asthma control was poorer in group 1 compared with group 2 as shown by a lower global ACSS score (mean ± SEM: 73 ± 3% and 82 ± 2%, respectively, p = 0.01). There were no differences in the clinical and inflammatory ACSS scores between groups although the physiological score was significantly lower (reduced expiratory flows) in group 1 (78 ± 4%) compared with group 2 (90 ± 3%, p = 0.02).

#### Spirometry

FEV<sub>1</sub> and FEV<sub>1</sub>/FVC were significantly lower in group 1 (mean ± SEM: 81 ± 3% and 70 ± 2%, respectively) than in group 2 (96 ± 3% and 76 ± 1%, p < 0.05 for both variables). These results are shown in Table 1.

#### Induced sputum

The results of induced sputum eosinophils are reported in Table 2. Eosinophil percentages and numbers per gram of mucus were higher in subjects with nasal polyposis than in

subjects without polyps (p < 0.05 and p < 0.01, respectively, see Table 2). Neutrophils (% and numbers per gram of mucus) were also higher in subjects with nasal polyposis (42.9 ± 4.3%; 3.4 ± 0.8 x 10<sup>6</sup> cells/g) than subjects without polyps (29.0 ± 3.4%; 1.1 ± 0.2 x 10<sup>6</sup> cells/g, p < 0.05).

Levels of VEGF, MMP-9, TIMP-1 and the ratio MMP-9/TIMP-1 were not different between the 2 groups. However, fibronectin and ECP levels were significantly higher in group 1 compared with group 2 (p < 0.05 for both parameters, see Table 2).

#### Blood eosinophils

Blood percentage and numbers of eosinophils were significantly higher in group 1 (p < 0.05, see Table 2), while percentage of lymphocytes was lower in this group (mean ± SEM: 26.1 ± 1.1 and 30.1 ± 1.0 for group 1 and 2, respectively, p < 0.05). Other inflammatory cells were not significantly different between the 2 groups.

#### Comparative results according to medication use

To assess the effects of ICS use on our results, we analysed the data within subgroups 1 and 2 for those subjects taking (A) or not (B) ICS for asthma. Groups 1A, 1B, 2A, and 2B included 24, 15, 20, and 20 subjects, respectively. Characteristics of those groups are shown in Table 3. Global and physiological ACSS scores were lower in subjects from group 1A compared with the other groups (p < 0.05). FEV<sub>1</sub> and FEV<sub>1</sub>/FVC were also lower in group 1A compared with the other groups (p < 0.05). Sputum eosinophil percentages and numbers per gram of mucus were significantly higher in subjects from group 1A compared with the other groups (p < 0.05 and p < 0.01, respectively). There were no differences between groups in mediator levels. Blood percentage of eosinophils were higher in subjects from group 1A compared with the 3 other groups (p < 0.05).

#### DISCUSSION

This study showed that, among asthmatic subjects, those with nasal polyps presented more poorly controlled asthma, increased airway obstruction and more marked lower airway inflammation than those without nasal polyps. These differences were mostly due to poorer outcomes in patients with nasal polyps concomitantly using ICS, despite a higher dose of ICS in these former, in addition to using nasal corticosteroids, compared with the group without nasal polyps.

Nasal polyposis and asthma are two chronic inflammatory disorders of the respiratory tract and these two entities are frequently associated, particularly in moderate to severe asthma<sup>(3)</sup>. In this regard, our results are in line with previous reports of an association between severe or difficult to control asthma and rhinosinusitis<sup>(2)</sup>.

Asthma and nasal polyposis have been linked to an impaired quality of life<sup>(24-26)</sup>. However, to our knowledge, this study is the first to assess the impact of nasal polyposis on asthma con-

Table 3. Subjects' characteristics according to medication use.

Group	1A	1B	2A	2B
n	24	15	20	20
Age (y)*	46±10 <sup>§</sup>	44±14 <sup>§</sup>	31±11	28±6
Gender (F/M)	13/11	8/7	13/7	13/7
Atopy (+/-)	19/5	9/6	20/0	20/0
Inhaled Beclomethasone or equivalent* (µg) <sup>‡</sup>	391±202 <sup>§</sup>	—	266±168	—
Nasal Mometasone or equivalent* (µg) <sup>‡</sup>	261±145	306±130	—	—
FEV <sub>1</sub> (% pred.) <sup>†</sup>	74±4 <sup>§</sup>	93±5	89±3	104±3
FEV <sub>1</sub> /FVC <sup>†</sup>	66±2 <sup>§</sup>	76±2	73±2	78±2
ACSS Score <sup>†</sup>				
Clinical	87±2	93±2	88±3	93±2
Physiological	73±5	86±5	84±5	95±3 <sup>§</sup>
Inflammatory	43±6 <sup>§</sup>	75±6	66±6	68±7
Global	67±4 <sup>§</sup>	84±3	79±3	85±3

Results are presented as means ± SD\* and as means ± SEM<sup>†</sup>. <sup>‡</sup>When applicable. <sup>§</sup>p < 0.05 vs the other groups. FEV<sub>1</sub>: forced expiratory volume in one second, FVC: forced vital capacity, ACSS: asthma control scoring system.

trol. The ACSS is a validated asthma control questionnaire<sup>(19)</sup> that assesses 3 different parameters involved in asthma: clinical, physiological and inflammatory. Although there were no differences in clinical and inflammatory scores, physiological score was significantly lower in subjects with nasal polyposis and asthma compared with subjects with asthma only. This resulted in a lower global control score in asthmatic subjects with nasal polyposis.

The physiopathology of nasal polyposis is still to be determined, but we know that these abnormal nasal mucosa outgrowths are mostly made of inflammatory cells, particularly eosinophils, which can produce and release various inflammatory mediators, cytokines and growth factors. Increased concentrations of ECP and interleukin (IL)-5 have been found in nasal lavage fluid<sup>(27)</sup>, nasal polyps tissue<sup>(28)</sup> and nasal secretions<sup>(28)</sup> of subjects with nasal polyps and asthma compared to subjects with nasal polyps but without asthma. These mediators could contribute to the lower airway inflammation by their release in the bronchial tract or by affecting it through the systemic circulation. Our results are in keeping with that, since we observed higher levels of sputum eosinophils, ECP, and fibronectin, as well as higher levels of blood eosinophils in subjects with nasal polyposis and concomitant asthma compared with subjects with asthma only.

Although it is possible that nasal polyps contribute to the severity of asthma, they may also only be markers of an increased susceptibility of the upper and lower airway mucosa to develop a more intense inflammatory response, in keeping with the "united airways" theory.

Previous studies demonstrated that eosinophil levels in bronchoalveolar lavage and bronchial biopsies were increased in subjects with nasal polyposis and symptomatic or asymptomatic airway hyperresponsiveness compared to subjects with nasal polyposis without airway hyperresponsiveness<sup>(9,10)</sup>. In this regard, our study adds new information, suggesting that a subgroup of asthmatic patients may have a more intense lower airway inflammation in relation with the presence of nasal polyps. Indeed, asthmatic subjects using ICS and having nasal polyps had a more intense inflammation and a poorer asthma control than asthmatic subjects not using ICS and having nasal polyps, reflecting a more severe subset of asthma. In addition, in subjects using ICS, nasal polyps seem to be a factor contributing to the worsening of asthma. Despite a higher dose, asthmatic subjects using ICS and having nasal polyps showed reduced asthma control and higher levels of inflammation than asthmatic subjects using ICS but without nasal polyps. This could be due to a more marked global airway inflammatory response, possibly reflecting a more aggressive type of nasal polyposis.

Table 4. Blood and sputum inflammatory parameters according to medication use.

Group	1A	1B	2A	2B
Sputum				
Eosinophils (%)	16.4±3.4*	11.0±0.8	3.8±1.1	4.0±1.3
Eosinophil count/g mucus (x10 <sup>6</sup> cells/g)	1.0±0.2 <sup>†</sup>	0.2±0.1	0.2±0.1	0.1±0.1
Levels of fibronectin (ng/ml)	353±90	230±61	126±24	149±39
Levels of ECP (ng/ml)	593±169	310±112	207±58	210±103
Blood				
Eosinophils (%)	6.6±0.8*	5.4±0.6	4.0±0.6	3.8±0.4
Absolute eosinophil count (x10 <sup>6</sup> cells)	0.5±0.07	0.4±0.04	0.3±0.05	0.3±0.04

Results are presented as means ± SEM. \* p < 0.05 vs the other groups. <sup>†</sup> p < 0.01 vs. the other groups. ECP: eosinophil cationic protein

We cannot exclude the effects of possible factors that might have interfered with the results. One possible confounding factor could have been that subjects from the polyp group were older. However, when analyzing the data according to medication, results from group 1B were not statistically different from groups 2A and 2B, although subjects from group 1B were older. Some authors observed differences in inflammatory and structural parameters in nasal polyposis subjects, based on atopic status<sup>(11,29)</sup>. Although most of our subjects were atopic, a sub-analysis of the results according to atopic status showed no differences between groups (data not shown). In this study, aspirin sensitivity was not recorded routinely. Subjects with aspirin intolerance show higher levels of arachidonic acid metabolites<sup>(30,31)</sup> and their receptors<sup>(32)</sup>. However, aspirin sensitivity does not seem to have an additional impact on the quality of life<sup>(26)</sup> or levels of inflammatory mediators<sup>(33)</sup> in subjects with nasal polyposis. We did not quantify the severity of rhinosinusitis; previous authors had suggested a relationship between the severity of chronic rhinosinusitis and the difficulty to control asthma<sup>(12)</sup>. A study looking at changes in the clinical and lower airway inflammatory parameters after surgical removal of nasal polyps would be of interest to clarify this relationship.

In conclusion, this study brings new information on the relationships between asthma control, physiological, and inflammatory parameters, in subjects with nasal polyposis, with or without asthma. It shows that nasal polyposis may be a major factor in the worsening of asthma, being associated with reduced asthma control, increased airway obstruction and higher airway inflammation. Furthermore, this is the first study to show that asthma severity plays a major role on the outcomes of those parameters. Despite its limitations, this study brings additional information on asthma features in the presence or not of nasal polyps and raises numerous questions on their relationships. Further studies should explore the mechanisms by which nasal polyposis may influence lower airways inflammatory processes.

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