Brief Communication:
Is Nasal Polyposis a Determinant of Bronchial Hyperresponsiveness and Altered Quality of Life in Asthmatic Subjects? A Case-Control Study.

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Abstract. Asthmatic patients with nasal polyposis (NP) have been reported to have a high prevalence of bronchial hyperresponsiveness (BHR) and a worsening of quality of life (QoL). The aim of this case-control study was to evaluate if NP is a determinant of BHR and is responsible for modifying the QoL in asthmatic subjects. Eighty-nine asthmatic subjects, including 24 patients with NP and 65 patients without NP (controls), underwent spirometry, methacholine challenge test (MCHt), skin prick tests, and were evaluated with the Asthma Quality of Life Questionnaire (AQLQ). Results of the MCHt test are expressed as the provocative concentration of methacholine that causes 20% (PC_{20}) fall of forced expiratory volume at 1 sec (FEV1). The PC_{20} (mean ± SD) in NP cases was 1149 ± 668 μg/ml vs 894 ± 691 μg/ml in controls (p <0.001). This demonstrates that BHR was not enhanced by the presence of NP in asthmatic subjects. No significant differences were found between the NP cases and controls for overall QoL or for single QoL domains. This study shows that the presence of NP did not impair the QoL of asthmatic patients, as indicated by the items included in the AQLQ questionnaire.

Keywords: asthma, bronchial hyperresponsiveness, nasal polyposis, methacholine test, quality of life

Introduction

Nasal polyposis (NP) is a chronic inflammatory disease of the paranasal sinus mucosa, leading to protrusion of edematous polyps into the nasal cavities, which may lead to nasal obstruction [1]. NP is associated with disorders of the lower respiratory tract, such as asthma and non-specific bronchial hyperresponsiveness (BHR) [2]. Among NP patients referred to an ear, nose, and throat (ENT) clinic, about 30% of patients had asthma [3]. Another study involving 445 patients with NP revealed that about 20% had asthma [4]. NP patients may present with BHR with eosinophilic bronchial inflammation that resembles inflammatory changes seen in patients with asthma, or without BHR, in which case they lack eosinophilic lower airway inflammation [5].

The pathogenesis of asymptomatic BHR is not fully understood, but pro-inflammatory cytokines and growth factors may play a role [6-8]. Clinically significant correlation has been established between results of the methacholine aerosolized challenge test and lower airway eosinophilic and mast cell infiltration [9,10]. The objective of our case-control study was to examine whether NP is a determinant of BHR and of worsening quality of life (QoL) in patients with asthma.
Materials and Methods

**Subjects.** From April 2003 to March 2004, we enrolled 89 asthmatic subjects who were non-smokers (65 males, 24 females), matched for body mass index (BMI), sex, and age, at our Respiratory Pathophysiology Center. The patients were considered asthmatic (n = 24) when the peak expiratory flow (PEF) increased more than 15% at 15-20 min after inhalation of a β2-stimulating short agonist (salbutamol 200 μg), as defined by the NHLBI/WHO criteria [11].

Asymptomatic (BHR) was defined as a methacholine PC_{20} ≤ 16 mg/ml in the absence of symptoms suggestive of asthma (intermittent wheeze, chest tightness, dyspnea, and recurrent cough) in subjects who did not report a history of childhood asthma and who had never required asthma medication [12]. Nasal polyps were identified in all patients by anterior rhinoscopy. Nasal symptoms associated with nasal polyps (obstruction, anosmia, sneezing, rhinorrhea, itching) were assessed.

Exclusion criteria for the study were as follows: emergency treatment for an asthmatic exacerbation within the past month; upper or lower airway infections in the last 8 weeks; current smoking habit, asthmatic exacerbation in the past 3 months; infectious sinusitis or previous history of nasal surgery; treatment with antihistamines, anticholinergics, teophyllin, colitis drugs, cromones, long-acting β2-stimulators, inhaled or oral corticosteroids in the past 4 months; presence of autoimmune, hepatic, or renal disorders, malabsorption, and drug- or alcohol-addiction; pregnancy or lactation; chronic bronchitis, emphysema, cystic fibrosis, bronchiectasis, gastroesophageal reflux, organic disease of gastrointestinal tract or related organs, or poor knowledge of the Italian language.

**Study design.** At each visit all subjects underwent a complete clinical check-up, skin prick tests for inhaled allergens and foods, pulmonary function testing, methacholine challenge test (MCHt), anterior rhinoscopy, and they completed the Asthma Quality of Life Questionnaire (AQLQ) of Juniper et al [13]. Informed consent was obtained from all subjects before enrollment and the study was approved by the University of Chieti Ethics Committee.

**Pulmonary function testing.** Patients completed at least 3 forced vital capacity (FVC) manoeuvres as indicated by the American Thoracic Society (ATS) standards [14]. For each group, we assessed forced expiratory volume at one second (FEV1), peak expiratory flow (PEF), and FVC.

**Methacholine challenge test.** The MCHt was performed according to the ATS protocol [12], using a dosimeter (Mefar MB3, Brescia, Italy) and starting by inhaling 6.25 μg/ml methacholine (lyophilised methacholine 6.4% Lofarma, Milan, Italy). After basal spirometry (the best among at least 3 significant tests) and inhalation of a buffered normal saline vehicle solution, patients inhaled increasing doses of methacholine up to a cumulative dose of 3.2 mg/ml; at the end of each inhalation of methacholine, a new FEV1 measurement was performed. The MCHt was considered positive when the amount of methacholine, defined as provocative concentration that caused a 20% fall in FEV1 (PC_{20}), was < 1.6 mg/ml. Basal FEV1 was obtained from the best of at least three significant tests (differences among the responses < 5%). The test was stopped when the FEV1 had decreased by at least 20% or when the maximum concentration (3.2 mg/ml) had been inhaled. The results were expressed as the provocation concentration causing a 20% decrease in the FEV1 (PC_{20}).

**Skin prick tests** (Lofarma, Milan, Italy) were performed on each subject using common antigens on the volar side of the forearm according to the Guidelines of the Subcommittee on Skin Tests of the European Academy of Allergy and Clinical Immunology. Histamine phosphate (10 mg/ml) and normal saline solutions were used as positive and negative controls, respectively. Prick tests were read after 15 min and were considered positive if the largest diameter of the swelling was 3 mm greater than the negative control.

**AQLQ.** Patients were asked to complete the AQLQ, which contains 32 questions in 4 domains: activity limitations, symptoms, emotional functions, and exposures to environmental stimuli [13]. For the domain of activity limitations, each patient was instructed to select 5 activities from a list of 26 that they expected to perform throughout the clinical trial. The other domains had standard response items. All items were rated on a scale ranging from 1 (maximal impairment) to 7 (no impairment).

**Statistical analysis.** Conventional analysis of measurements of methacholine airway responsiveness compared PC_{20} values. The PC_{20} values were calculated by extrapolation using log-transformed data. Continuous variables were reported as means ± SD. Categorical variables were reported as counts and percentages. Differences between groups with respect to demographic variables were evaluated using the Chi-square test for categorical variables and the independent sample t-test for continuous variables. For analysis of the AQLQ, responses to individual questions were first grouped into 4 domains of questions relative to QoL. The rank for the responses to each question was a score from 1 to 7. The ranks for each subject were summarized and divided by the number of questions in the set defining the score. This calculation provided an average rank for each subject and for all items of the domain. Median ranks and inter-quartile ranges (25%-75%) were computed and one-way, non-parametric analysis (Kruskal-Wallis test) was used for overall comparisons among the four domains of QoL. The Mann-Whitney test was used for unpaired comparisons. All statistical analyses were performed using SPSS version 10.05 (SPSS, Inc., Chicago, IL) and statistical significance was defined as p < 0.05.

**Results**

**Basal characteristics.** Personal data of patients (sex, age, and BMI), spirometric values (FEV1, FVC, and PEF), and PC_{20} concentrations are listed in
Table 1. Characteristics of the 89 asthmatic subjects, including 24 cases with nasal polyposis (NP) and 65 without NP.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NP Cases</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>24</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Females/males</td>
<td>7/17</td>
<td>17/48</td>
<td>ns</td>
</tr>
<tr>
<td>Spirometric values*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>99.7 ± 8.5</td>
<td>101.8 ± 7.6</td>
<td>ns</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>102.2 ± 8.1</td>
<td>100.5 ± 11.0</td>
<td>ns</td>
</tr>
<tr>
<td>PEF (% predicted)</td>
<td>106.0 ± 8.3</td>
<td>101.9 ± 11.2</td>
<td>ns</td>
</tr>
<tr>
<td>PC_{20} mg/ml</td>
<td>1.15 ± 0.67</td>
<td>0.89 ± 0.69</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* mean ± SD

Table 2. Scores for quality of life (QoL) in 89 asthmatic subjects, with or without NP, assessed by the AQLQ questionnaire.

<table>
<thead>
<tr>
<th>Quality of life domains</th>
<th>No. of items</th>
<th>NP Cases (n = 24)*</th>
<th>Controls (n = 65)*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All domains</td>
<td>32</td>
<td>5.46 ± 1.43</td>
<td>5.37 ±1.22</td>
<td>ns</td>
</tr>
<tr>
<td>Physical activity</td>
<td>11</td>
<td>5.46 ± 1.19</td>
<td>5.45 ± 1.13</td>
<td>ns</td>
</tr>
<tr>
<td>Symptoms</td>
<td>12</td>
<td>5.27 ± 1.59</td>
<td>5.13 ± 1.36</td>
<td>ns</td>
</tr>
<tr>
<td>Emotions</td>
<td>5</td>
<td>5.78 ± 1.58</td>
<td>5.65 ± 1.46</td>
<td>ns</td>
</tr>
<tr>
<td>Environmental stimuli</td>
<td>4</td>
<td>5.57 ± 1.43</td>
<td>5.46 ± 1.53</td>
<td>ns</td>
</tr>
</tbody>
</table>

* mean ± SD

Table 1. There were 89 subjects (65 males and 24 females), including 24 NP cases with mean age of 37 ± 14 yr and 65 controls with a mean age of 25 ± 8 yr. The BMI of the study population was 24.4 ± 3.9 kg/m² for NP cases, and 23.4 ± 3.6 kg/m² for controls; these data did not differ significantly. Spirometric values of all subjects were 100% of predicted values and there were no statistically significant differences between NP cases and controls. The value of PC_{20} was 1.15 ± 0.67 mg/ml in NP cases and 0.89 ± 0.69 mg/ml in the controls, with a statistically significant difference (p < 0.001) (Table 1).

**Asthma Quality of Life Questionnaire.** The mean ± SD scores for QoL, evaluating the individual and the combined domains, are shown in Table 2. In the group of NP cases, the subjects had a total score of 5.46 ± 1.43 for all items, compared to 5.37 ± 1.22 in the control group. For the physical activities domain, the mean score was 5.46 ± 1.19 (NP cases) compared to 5.45 ± 1.13 (controls). Scores for the symptoms domain and the emotions domain were 5.27 ± 1.59 and 5.78 ± 1.58 (NP cases) compared to 5.13 ± 1.36 and 5.65 ± 1.46 (controls) respectively. For the environmental stimuli domain, the mean score was 5.57 ± 1.43 (NP cases) compared to 5.46 ± 1.53 (controls).

**Discussion**

In this study we evaluated two important aspects of patients with nasal polyposis (NP) compared with controls. The first aspect regards the BHR tested with methacholine. We found a significantly lower PC_{20} value in controls compared to NP cases. This demonstrates that BHR is not determined by the presence of NP in asthmatic patients, but may represent a simple characteristic of bronchial asthma, even if several studies have reported that patients with NP and no clinical evidence of bronchial asthma commonly exhibit nonspecific BHR when tested with methacholine [15-18].

Studies have suggested the presence of a subclinical bronchial eosinophilic process associated with BHR in upper airway diseases such as allergic rhinitis, nonallergic rhinitis with eosinophilic syndrome (NARES), and NP [9,15,19]. The clinical relevance of the presence of asymptomatic BHR is unknown. It has been proposed that BHR could be a risk factor for the subsequent development of asthma [20,21]. In our study NP may represent an adjunctive complication in patients with bronchial asthma [22-24]. Even if NP represents a chronic eosinophilic inflammatory disorder of the nasal and paranasal sinuses that leads to the formation of benign polyps, when systematically assessed, nonspecific BHR is not commonly measurable in asthmatic patients with NP. Asymptomatic BHR may be a preliminary stage before the development of asthma, as reported in many studies [25].

The second aspect concerns the QoL. NP is frequently associated with chronic inflammatory disease of the upper respiratory tract, which may worsen the QoL and is often associated with lower respiratory disorders [26,27]. A study in which the generic SF-36 questionnaire was completed by 49 consecutive patients with NP indicated that NP
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impaired QoL to a greater degree than perennial allergic rhinitis [17]. Our study shows that in asthmatic patients the presence of NP does not impair QoL in any or all of the domains included in the AQLQ questionnaire.

Whether inflammation secondary to NP may contribute to the presence of BHR in asthmatic subjects and whether the QoL of asthmatic subjects is influenced by NP merits further investigation.

References