Immunologic Factors in Patients with Chronic Polypoid Sinusitis

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Abstract
Background: Nasal polyposis is the benign protrusion of soft tissue into the nasal cavity, with multifactorial origin. This study is designed to examine the suggested role of IgE and CD4 and CD8 lymphocytes in the pathogenesis of nasal polyposis.
Methodology: Blood samples were taken from 32 patients with chronic polypoid sinusitis and 32 controls. CD4 and CD8 total lymphocyte count were determined by flow cytometry and the level of serum IgE was measured by ELISA. Nasal discharge samples were also collected for determining IgE level in both patients and controls during surgery.
Results: In 68.8% of patients a history of allergy was present. The level of nasal discharge IgE was significantly higher (p<0.001) in patients compared to controls, but the difference between serum IgE levels was not significant (p> 0.05). CD8 concentration and blood lymphocytes were significantly higher (p<0.001) in the patients group, while CD4 concentration was significantly lower (p<0.001) in them. Finally, CD4/CD8 ratio was significantly lower (p<0.001) in the patients group.
Conclusion: This study suggests that a change in the amount of CD4 and CD8 lymphocytes and an increased level of local IgE contribute to nasal polyposis, but the results should be confirmed in more extensive studies including cytokine analyses. Such increasing insights in the pathophysiology of nasal polyposis open perspectives for new pharmacological treatment options, with immunologic factors as potential targets.
Keywords: Nasal polyposis, CD4, CD8, IgE

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Introduction
The history of nasal polyps dates back to over three thousand years ago in India, where a type of curette was described for eradicating nasal polyps. Nasal polyps are seen in patients of all ages. They are present in approximately 2% of the general population. There is at least a 2:1 male to female predominance. The frequency of nasal polyps increases with age, reaching a peak in individuals 50 years and older. Nasal polyposis is not a disease, but a physical finding with a number of causes and associated conditions. Most commonly, 25%-30% of patients have asthma, while approximately 12% have aspirin intolerance. Nasal polyps are also seen in 0.1% of children and 20% of patients with cystic fibrosis. They are seen in 50% of patients with eosinophilic vasculitis of Churg Strauss syndrome. They are also seen in disorders of ciliary motility like Kartagener’s syndrome, as well as other genetic syndromes such as Young’s syndrome, which is a bronchopulmonary disease accompanied by azoospermia.

Proposed mechanisms implicated in the development of nasal polyps include: allergy, infection, autonomic imbalance, mucopolysaccharide abnormalities, enzyme abnormalities, drug sensitivity and mechanical obstructions.

Nasal polyps consist of respiratory epithelium covering a very edematous stroma infiltrated by a large number of inflammatory cells with eosinophils being the predominant group. Bilateral nasal polyposis is associated with concentrations of IgE in nasal polyp tissue. Infiltrated mast cells demonstrate ultra structural signs of degranulation, associate with continuous release of histamine, which is found in higher concentrations in polyp fluid.

The presence of controversies in previous studies that evaluated the lymphocyte subpopulations and their production of cytokines and IgE in serum and nasal secretion in order to elucidate the role of immunologic
factors in the process of nasal polyps as well as difference in their results lead us to do further investigations. So in this sequel, this study is designed to examine the suggested role of IgE, and CD4 and CD8 lymphocytes in the pathogenesis of nasal polyposis.

Patients and Methods
Seventeen men and 15 women, ranging in age from 20 to 71 years (mean, 46.6 years), who had chronic rhinosinusitis with diffuse nasal polyps and underwent endoscopic sinus surgery, were included in this study. All of the patients gave written informed consent and the study was approved by the Institutional Review Board and ethics committee of Ahwaz Jondishapour University of Medical Sciences. The demographic data of the study and control groups have been given in the Table 1. The Peripheral blood samples were taken from 32 patients for whom the diagnosis of chronic polyoid sinusitis was established, and 32 control patients who were candidates for septoplasty who had a negative history of allergy and sinusitis. The samples were sent to laboratory for lymphocyte count and determination of amounts of CD4 and CD8 lymphocytes by flow cytometry (Becton Dickinson Co., USA), and serum IgE by ELISA. Nasal discharge samples were also collected for determining local IgE level in both patients and controls during surgery.

Monoclonal antibodies used in flow cytometry analysis included fluorescein isothiocyanate (FITC) and phycoerythrin (PE) -conjugated against CD4 and CD8 markers (Dako Co., Danmark). All samples were washed in sodium perborate (PBS) after staining procedures, followed by exposure to a lysing reagent again. FITC and PE-conjugated mouse IgG1 were incubated with cells obtained from Patients in parallel to negative controls. Prepared immunostaining cell suspensions were submitted to flow cytometry analysis. IgE levels were measured in serum and nasal discharge samples using a kit prepared from PAD TANELAM Company of Iran, and were recorded based on international units per milliliter (IU/ml).

Statistical analysis:
The data obtained were analyzed statistically using the t-test. P-values less than 0.05 were considered as significant.

Results
IgE level of nasal discharge was significantly higher (p<0.001) in patients compared to the control group; it was 84.6 IU/ml in the patients group and 5 IU/ml in the control group. Also the difference in serum IgE was not significant (p>0.05) with a values of 130.5 IU/ml in Patients and 127.6 IU/ml in controls (Table 2). In 68.8% of patients a history of allergy was present. CD8 concentration (46.8% in patients vs 28.3% in controls) and percentage of peripheral blood lymphocytes (17.7% in Patients and 31.6% in controls) were significantly different (p<0.001 for both comparisons) between the two groups (Table 2). Ironically, CD4 concentration was significantly lower (p<0.001) in patients (Table 2). Finally, CD4/CD8 ratio was significantly lower (p<0.001) in the patients (Table 2).

Table I: Demographic and immunological features of patients and control groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n=32)</th>
<th>Control (n=32)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (year)</td>
<td>48</td>
<td>46</td>
<td>0.341</td>
</tr>
<tr>
<td>Gender (Male: Female)</td>
<td>15:17</td>
<td>13:19</td>
<td>1.0</td>
</tr>
<tr>
<td>Elevated serum IgE (frequency)</td>
<td>22 (68.75%)</td>
<td>3 (9.37%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood eosinophilia</td>
<td>27 (84.37%)</td>
<td>2 (6.25%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lymphocytes (Mean ± SD)</td>
<td>31.69 ± 7.07</td>
<td>17.72 ± 5.96</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Discussion
Although the etiology of nasal polyposis is still not revealed, insights in the pathogenesis have largely expanded over the last years. There are two models suggested for the development of nasal polyposis: one states that this condition is caused by the up-regulation of cytokines leading to increased eosinophil degranulation; the other mechanism suggests that injury to the airway epithelial cells induced by an allergen, viruses or trauma leads to defective transmembrane regulators, which in turns alters sodium chloride flux in the epithelial cell and finally directs to edema.

A consistent feature in nasal polyposis is a prominent infiltration of inflammatory cells, and it has been proposed that alteration of immune regulation could be implicated as a contributing factor. The eosinophil leukocyte is the dominant cell in polyps; consequently,
allergy has been considered as an important etiology for nasal polyps. The prevalence of allergy in patients with nasal polyps varies from 10% to 54%. There is a coincidence of asthma and nasal polyps but the association between polyposis and atopic conditions is not clear. It has been newly suggested that Staphylococcus Aureus may have a role in formation of nasal polyps. This pathogen is found in the nasal samples obtained from these patients, although the significance is unclear. The bacteria may secrete exotoxins that act as superantigens and are a possible trigger for local IgE production in nasal polyps.

It should be emphasized that the presence of eosinophils in the polyps does not depend on the presence of allergy or IgE-mediated hypersensitivity disorders, but is related to up-regulation of appropriate cytokines and growth factors such as interleukin-1ß, tumor necrosis factor, macrophage colony stimulating factor. All these cytokines have direct or indirect effects on the transmigration of eosinophils from the microvasculature into the lamina propria of nasal polyps. In one study, Bernstein et al. showed that two subpopulations of lymphocytes, CD4 and CD8, have significant roles in production of these cytokines. Their findings imply that there are significant differences between the percentage of lymphocytes producing these cytokines in nasal polyps and peripheral blood. Lymphocytes infiltrated in nasal polyps may derive from a source other than peripheral blood. They may be derived from both the local mucosal immune system as well as from random migration of peripheral blood lymphocytes.

Ihan and Suskovic evaluated CD4 and CD8 cells isolated from nasal tissue in allergic and nonallergic polypoid sinusitis, and found a significant increased expression of intercellular adhesion molecule-1 (ICAM-1) molecules on CD8 cells in nonallergic compared to allergic patients. This finding may reflect the difference in cytotoxic immune response between allergic and nonallergic patients, although it is inconsistent with the result of a study by Hel, in which the expression percentage of CD3+, CD4+ cells appeared to be significantly higher than that of CD3+, CD8+ cells.

A survey conducted by Muluk implies on the role of T-helper lymphocytes in the pathophysiology of chronic sinusitis, and CD4+ T-helper cells in particular are thought to be predominant at the initiation and regulation of inflammation.

Our study shows that a change in the amount of CD4 and CD8 lymphocytes and an increase in the level of local IgE to be important, which suggests that local allergy may play a key role in sinonasal polyposis; however, the results should be confirmed in more extensive studies which recruit cytokine analysis. Increasing insights in the pathophysiology of nasal polyps let us gain open perspectives for new pharmacological options with CD4 and CD8 lymphocytes and local IgE secretion as potential targets for treatment. We hope that it would enable us to obtain a deeper insight into the local immune events and further to clarify the etiology and pathogenesis of nasal polyps and their relation to allergy.

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References


