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Interleukin-4, Interleukin-8 and E-selectin Levels in Intranasal Polyposis Patients with and without Allergy: a Comparative Study

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Intranasal polyposis is a chronic inflammatory upper airway disease with unknown aetiology. Interleukin (IL)-4 and IL-8 play very significant roles in allergic events and infectious inflammation, respectively. In contrast, E-selectin is important in the initiation and organization of inflammation. In this study, levels of IL-4, IL-8 and E-selectin were measured in nasal mucosa specimens of intranasal polyposis patients with and without allergic rhinitis, and healthy controls. Healthy controls had significantly higher IL-4 levels than allergic patients and non-allergic patients; IL-4 levels were similar in allergic and non-allergic patients. Allergic and non-allergic patients had significantly higher IL-8 levels than healthy controls; IL-8 levels were comparable in allergic and non-allergic patients. E-selectin levels were similar in all groups. The infection-based theory, represented by IL-8, seems to be more likely than the allergy-based theory, represented by IL-4, for the pathogenesis of nasal polyposis.

KEY WORDS: Nasal polyposis; Interleukin-4; Interleukin-8; E-selectin; Allergy

Introduction

Intranasal polyposis is a chronic inflammatory upper airway disease. It may be accompanied by other clinical entities and may be present in various clinical forms. Therapeutic success is still limited in intranasal polyposis, and the development of new and more effective therapeutic modalities requires thorough investigation of the underlying pathophysiology. Interestingly, eosinophilia-related cytokines are found in high amounts in polypoid tissues and $CD4^+$ T-lymphocytes are elevated in patients with nasal polyposis and allergy.[1]

Interleukin (IL)-4 and IL-8 play very significant roles in allergic events and infectious inflammation, respectively. E-selectin is important in the initiation and organization of inflammation. The aim of

this study was to examine the roles of IL-4, IL-8 and E-selectin in the pathophysiology of intranasal polyposis in allergic and non-allergic patients.

Patients and methods

PATIENTS

Permission to perform the study was given by the ethics committee of Gazi University Faculty of Medicine Hospital and each patient gave written informed consent. Intranasal polyposis patients, both allergic and non-allergic, and healthy controls were enrolled in the study. The diagnosis of intranasal polyposis was reached by reference to the patient's detailed history, complete otolaryngological examination, and anterior rhinoscopy and nasal endoscopy. The presence of polyps in the middle meatus was essential for the diagnosis of intranasal polyposis. A skin-prick test kit (Stallergenes, Institut Pasteur, Paris, France) was used to test for atopy. The kit included allergens from mites, fungi, animal epithelium, pollens and cereals. Oedema at the application point was evaluated after 15 min. Responses to the skin-prick test were compared with a histamine-positive control (10 mg/ml) and a diluted antigen-negative control. The size of the oedema was calculated by taking the mean of the horizontal and vertical diameters. Reactions with a mean size of at least 3 mm were accepted to be positive. Patients who revealed atopy in their history and who had a positive reaction to at least one of the allergens in the skin-prick test were classified as 'allergic'. Patients enrolled in this study had not undergone any surgical intervention for intranasal polyposis and they had not been given any medical treatment, such as macrolides and local or systemic corticosteroids.

METHODS

After decongestion and topical anaesthesia of the nostrils with pantocaine and adrenaline, nasal biopsies were taken endoscopically from the polyps of the patients and from the middle turbinate tissues of healthy individuals with 5 cm Trucut forceps (Smith & Nephew, Memphis, Tennessee, USA). Levels of IL-4, IL-8 and E-selectin were measured by an enzyme-linked immunosorbent assay method using commercial kits (Bender Med Systems, Vienna, Austria for IL-8 and E-selectin; Biosource International, California, USA for IL-4). The cytokine profiles of the allergic and the non-allergic patients were compared with each other and with the control group.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS® version 11.0; SPSS Inc., Chicago, Illinois, USA). Since the groups were independent of each other, the non-parametric Kruskal–Wallis test was used. *P*-values < 0.05 were considered to be statistically significant.

Results

Thirty-five patients with intranasal polyposis (20 allergic and 15 non-allergic) and 12 healthy controls took part in the study. There was no statistically significant difference between the groups with respect to age and gender. IL-4, IL-8 and E-selectin levels for the three groups are given in Table 1. The healthy controls had significantly higher IL-4 levels than allergic patients and non-allergic patients ($P < 0.05$); IL-4 levels were comparable in allergic and non-allergic patients.

Allergic and non-allergic patients had significantly higher IL-8 levels than healthy controls ($P < 0.05$), while IL-8 levels were similar in allergic and non-allergic patients. E-selectin levels showed no significant differences between groups.

TABLE 1:
Levels of interleukin-4, interleukin-8 and E-selectin in intranasal polyposis patients who were allergic or non-allergic in a skin-prick test, and in healthy controls. Nasal biopsies were taken from the polyps of the patients and from the middle turbinate tissues of the healthy controls

	Allergic patients (*n* = 20)	Non-allergic patients (*n* = 15)	Healthy controls (*n* = 12)
Interleukin-4 (pg/ml)	2.30 ± 10.29[a]	3.28 ± 12.70[a]	6.67 ± 16.34
Interleukin-8 (pg/ml)	116.10 ± 237.07[a]	174.84 ± 326.24[a]	30.54 ± 80.41
E-selectin (pg/ml)	3.95 ± 1.14	3.68 ± 1.56	4.18 ± 0.66

Values are mean ± SD.
[a]$P < 0.05$ versus healthy controls.

Discussion

Intranasal polyposis is a frequent and highly morbid disease that diminishes quality of life and productivity. More than one factor is thought to be responsible for the pathogenesis of intranasal polyposis, and consequently treatment should be directed to the local tissue pathology and the underlying inflammatory process. Mucosal epithelium, matrix and inflammatory cells participate in an integrated manner in the formation and growth of polyps after pathological stimulation.

Interleukin-8 levels were higher in intranasal polyposis patients, regardless of the presence of allergy. Di Lorenzo *et al.*[2] demonstrated the presence of IL-8 in all intranasal polyposis tissues and speculated that it played an important role in pathogenesis, a role that is not thought to be restricted to the early stage of inflammation. Therefore, IL-8 may be involved in the pathogenesis of intranasal polyposis, possibly via a mechanism separate from its action in the regulation of infection. The effects of macrolides and steroids in suppressing IL-8 levels produced by eosinophils, human nasal epithelial cells and exudative cells in nasal discharge are explained by the conclusions of Cervin[3] and Wallwork *et al.*[4] The capability of eosinophils in polypoid tissue to synthesize IL-8 is still doubtful. In the present study, IL-8 levels in polypoid tissue were found to be higher than those in controls, so local synthesis of IL-8 in the nasal mucosa may be possible.

Naclerio[5] stated that IL-8 synthesis occurred in the late stage of the allergic response and that this synthesis was important in the regulation of allergic reaction; however, no difference was found among intranasal polyposis patients with respect to allergy in this study. This may have been due to the possible role of IL-8 in the pathogenesis of intranasal polyposis by a mechanism other than its function in the late-stage response. IL-8 suppresses immunoglobulin E (IgE) production[6] and it may be assumed that polyp formation occurs via a non-IgE-mediated reaction. The IL-8 level is high in patients with acute and chronic rhinosinusitis; it increases the recruitment of leucocytes, especially neutrophils.[7] Polyposis may result in a predisposition to infection, and one explanation for the high IL-8 levels in intranasal polyposis may be an increased tendency to infection in these patients. An increase in the IL-8 level may point to possible roles of monocytes and

T-lymphocytes, in addition to eosinophils.[6] On the other hand, the contribution of infection to polyp formation is still unknown; some authors have proposed that increases in the levels of cytokines in intranasal polyposis are related to the increase in the surface area of the nasal mucosa.[2]

Interleukin-4 levels were found to be higher in the control group than in the intranasal polyposis patients regardless of allergy status. Allergy is not thought to have an important role in the pathophysiology of intranasal polyposis;[8,9] however, it may be wrong to assume that IL-4 has no role in the pathogenesis of intranasal polyposis. Low levels of IL-4 may result from depletion of stores due to continuous stimulation. Modulation of the inflammation is directed by mast cells in the acute phase but by activated T-lymphocytes in the later stage.[10] The level of an inflammatory mediator may vary during different stages of inflammation. The stage of inflammation at the time of biopsy is therefore an important determinant of cytokine levels. Patients enrolled in this study were mostly at the late stage of chronic inflammation; therefore, care must be taken in the interpretation of the results. IL-4 is synthesized by mast cells in the early stages of allergic inflammation and it increases the expression of adhesion molecules such as E-selectin, which provide the continuity of chronic inflammation.[10,11] Suzuki *et al.*[6] claimed that IL-4- and IgE-mediated reactions were important for the development of intranasal polyposis, and Di Lorenzo *et al.*[2] demonstrated the presence of IL-4 in all polypoid tissues. The reason that there was no difference between allergic and non-allergic patients in this study may be that IL-4 controls the IgE-related mediator release from mast cells and helps the eosinophilic infiltration of nasal mucosa.[12] In contrast, de Vries[13] speculated that IgE-mediated reactions and allergic responses were regulated primarily by IL-13 rather than IL-4.

E-selectin levels were similar in all three of our groups, consistent with the data of Liu *et al.*,[14] but the suppressive effects of IL-8 on E-selectin[15] and the biphasic release of this molecule (an increased level in the acute phase and a decreased level in the late phase) must be remembered. Interruption of the inflammatory cascade in the early stages may be achieved if adhesion molecules can be blocked effectively. Naclerio[5] found that E-selectin levels were higher in the early stage of inflammation in the vascular endothelium; E-selectin is known to exist in stimulated endothelial cells in the first few hours, and its level starts to decrease after about 24 h.[5] Patients admitted to this study were at an advanced stage of inflammation, so it may not be entirely justifiable to conclude that E-selectin has no role in the pathogenesis of intranasal polyposis. Steroids are used commonly in the treatment of intranasal polyposis and act by suppressing the levels of cytokines, in particular IL-4 and IL-5.[14] Hence, it is suggested that a non-IgE-mediated process resembling the late-stage allergic reaction may play a role in the pathogenesis of intranasal polyposis.

In conclusion, the infection-based theory, represented by IL-8, seems to be more likely than the allergy-based theory, represented by IL-4, as an explanation of the pathogenesis of nasal polyposis. In order to understand the pathogenesis and develop more effective therapies, however, the complex network of neuromediators needs further investigation in prospective studies.

Conflicts of interest

No conflicts of interest were declared in relation to this article.

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