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ORIGINAL ARTICLE

Olfaction and Its Correlates in Allergic Rhinitis: A Case Control Study

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Abstract Olfactory dysfunction is frequent in rhinological disease. It has been attributed to nasal obstruction leading to impairment of transport of odorants to the olfactory epithelium or to inflammation in the olfactory cleft. We assessed olfaction in allergic rhinitis and correlated the olfactory score with other variables; in order to elucidate the pathogenesis of olfactory impairment in allergic rhinitis. Forty patients of allergic rhinitis (skin prick test positive) and forty healthy controls were included. The groups were evaluated for olfactory score, nasal airflow, peripheral eosinophilia, and levels of IgE and IL-5 in nasal secretions. The combined olfactory score in the patients was lower than that in controls. The score was better in patients with a better nasal airflow, but no significant association was found between the two. The peripheral eosinophilia and IgE and IL-5 level in nasal secretions was significantly higher in patients but demonstrated no significant correlation with the olfactory score. Allergic rhinitis patients had a decreased olfactory score; which weakly correlated to the nasal airflow. Local IgE and IL-5 were elevated in allergic rhinitis but did not show a significant correlation with olfactory scores. Our study concludes that both factors exist in allergic rhinitis but which factor is significantly responsible for hyposmia is not clear.

Keywords Olfaction · Allergic rhinitis · Hyposmia · Inflammatory markers

Introduction

Allergic Rhinitis is an inflammatory disease of the nasal mucosa. It typically affects 10–25% of worldwide population [1]. Olfactory impairment is a frequent symptom in allergic rhinitis patients. In a recent review of studies pertaining to olfaction in allergic rhinitis it was reported that the frequency of olfactory dysfunction increases with the duration of the disorder and hyposmia is reported in 20–40% patients of allergic rhinitis [2].

The proposed mechanism for olfactory dysfunction in nasal and sinus disease is either an anatomical abnormality leading to nasal obstruction and impairment of transport of odorants to the olfactory epithelium or inflammation in the olfactory cleft leading to decreased olfaction. The exact pathophysiology of olfactory impairment in allergic rhinitis is still not clear [3].

Since allergic rhinitis is an IgE mediated type 1 hypersensitivity reaction which has been shown to have a typical helper T-cell type 2 (Th2) profile along with local overproduction of type 2 cytokines and tissue eosinophilia [4], Immunoglobulin E and IL-5 (for its role in tissue eosinophilia) were chosen as markers to obtain more information about the mechanism of olfactory impairment in allergic rhinitis. Our goal was to correlate the olfactory score of patients with their clinical profile, nasal airflow, peripheral eosinophilia, serum IgE and levels of IgE and IL-5 in nasal secretions.

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For an objective estimation of nasal airflow we performed active anterior rhinomanometry, which is a well established, useful clinical method for objective evaluation of nasal patency and has contributed to an understanding of nasal physiology [5].

Allergic Rhinitis has been also found to be associated with increase in levels of nasal NO as compared to healthy individuals [6]. It is a gas produced by a family of enzymes, nitric oxide synthases (NOS) that use L-arginine as substrate. It is secreted in the respiratory tract with a major contribution from the upper airways especially the paranasal sinuses. It has been reported as a marker of inflammation in the airways therefore we aimed to study its correlation with the olfactory score in our patients.

Methods

We evaluated patients presenting with clinical features suggestive of allergic rhinitis. Forty patients of allergic rhinitis (skin prick test positive) (group A); were consecutively included in the study. Patients in the age group (18–50 years) with 2 years or more of symptoms of perennial allergic rhinitis were included. Patients with nasal polyps, history of immunotherapy in past 3 years, history of antihistaminic or steroid intake in the past 2 weeks, history of head trauma and chronic smokers were excluded from the study. None of the patients had history of asthma, urtiaria or any other atopic disease. Forty healthy controls (group B) were assessed for olfactory score, nasal airflow and levels of inflammatory markers in nasal secretions. The study was approved by the institutional ethical committee and all patients and controls gave an informed consent to the study.

Olfactory function was tested using the olfactory threshold and olfactory identification test scores, the total of which was the combined olfactory score (COS). Various tests have been described to test olfactory function [7–11]. The methodology followed by us was according to a previously tested and validated olfaction test which was a modification of CCCRC and COT test for the local population [12]. Threshold testing was performed using 1-butanol solution of different successive dilutions using a standard technique. Odour identification testing was done using ten odours namely asafoetida, naphthalene, garlic, vicks vaporub, rose water, sandalwood oil, cardamom, clove oil, lemon and cumin seeds.

Nasal airflow was measured using rhinomanometry [13]. Biochemical investigations of special significance included serum IgE and absolute eosinophil count.

Nasal secretions were obtained by placing cone shaped cotton wool pieces into the middle meatus of the nose under endoscopic view for 10 min, followed by centrifugation of the cotton wool pieces at 2000 g for 10 min. The samples were stored at −80 degrees [14]. Levels of IgE (Human anti IgE ELISA, KOMA BIOTECH, Seoul, Korea) and IL-5 (Human anti IL-5 ELISA Kit, KOMA BIOTECH, Seoul, Korea) were then detected using ELISA method. Since IL-5 cannot be reliably measured in human serum, it was determined in nasal secretion only.

Niox Mino® (Aerocrine AB, Sweden) was used to measure fractional exhaled nitric oxide in 28 out of forty cases (group A). Patient was asked to inhale deeply and then exhale through the disposable filter. The level of nitric oxide in parts per billion units was recorded for analysis.

Statistical analysis was performed using SPSS for windows. All analyses were performed using two-tailed test significance at the $p < .05$ level. Spearman correlation coefficients were used to examine the correlation between combined olfactory score, nasal inspiratory flow, serum IgE levels, peripheral eosinophilia and IgE and IL-5 levels in nasal secretions.

Results

The combined olfactory score (COS) in the patient group ranged from 14.60 ± 2.24; while that in controls ranged from 18.70 ± 2.33. Though difference in COS in the two groups was statistically significant, subjective complaint of hyposmia was infrequent in patients. Patients were more troubled by the nasal stuffiness, excessive sneezing and nasal discharge; and reported hyposmia less frequently.

The mean absolute eosinophil count in patients was 730.43 cells/mcl ± SD 769.21; while that in controls was 128.88 cells/mcl ± SD 89.03. The difference was statistically significant. The nasal IgE level was 25.4 ng/ml (10.6–41.07) in the allergic rhinitis patients and was 0.009 ng/ml (.003–.037) in the healthy controls. The level of nasal IL-5 was 2.69 pg/ml (1.72–5.35) in cases and .0275 pg/ml (.0036–.0495) in controls. The mean serum IgE in cases was 349.28 ± 167.235 lU/ml. The average peak nasal inspiratory flow in patients of allergic rhinitis was 403.10 l/min ± 83.64 and the value was 504.73 ± 98.26 in healthy controls. All these parameters are presented in Table 1.

On analysis of correlation coefficient values between olfactory score and other variables; COS showed poor correlation with other variables. On applying Pearson correlation formula, the olfactory score was better in patients with a better nasal airflow ($r = .043$), but the association was not significant ($p = .794$). The peripheral eosinophilia, IgE and IL-5 level in nasal secretions were significantly higher in patients but there was no statistically significant correlation with the olfactory score; the spearman coefficients of correlation being ($\rho = -.188$, $p = .246$), ($\rho = .039$, $p = .811$) and ($\rho = -.243$, $p = .131$) respectively, as shown in Table 2.

Table 1 Comparison of parameters in cases and controls

	Cases	Controls
Combined olfactory score	14.60 ± 2.24	18.70 ± 2.33
Mean absolute eosinophil count	730.43 cells/mcl ± SD 769.21	128.88 cells/mcl ± SD 89.03
Nasal IgE level	25.4 ng/ml (10.6–41.07)	.009 ng/ml (.003–.037)
Nasal IL-5 level	2.69 pg/ml (1.72–5.35)	.0275 pg/ml (.0036–.0495)
Average peak nasal inspiratory flow	403.10 l/min ± 83.64	504.73 l/min ± 98.26

Skin prick test (SPT) was done in all 40 cases of allergic rhinitis. Patients were tested with 58 aeroallergens [15]. The results of skin prick tests indicated that the main allergens in our study were cockroach (25%) followed by mosquito (21.6%).

Fractional exhaled nitric oxide (FENO) was measured in 28 cases positive for SPT, out of which only 8 showed elevated levels. Rest of the cases showed values within normal range (5–20 ppb). The mean FENO score of 28 patients was 16.854 ppb ± 13.09. On correlation with the olfactory score, no significant correlation was seen amongst the two variables ($\rho = .003$, $p = .989$).

Discussion

Quality of life is negatively correlated with olfactory dysfunction [16]. Allergic rhinitis is a common morbid condition; however among all symptoms of allergic rhinitis hyposmia is probably the least reported and investigated. To date there exist only few systemic studies regarding olfactory function in allergic rhinitis [1, 17, 18].

Apter et al. [17] while reporting on their study reported that, there appears to be a continuum of duration and severity of olfactory loss in allergic rhinitis that parallels increasing severity of nasal sinus disease. The self reported duration of olfactory loss increased significantly with nasal sinus disease severity. Since in our study, none of the patients suffered from chronic rhinosinusitis or nasal polyps so perhaps hyposmia was reported less frequently. None of our patients reported fluctuations in olfactory sensitivity or distorted olfactory perception unlike this study. The olfactory cleft visibility was used as a crude measure of nasal obstruction by Apter et al. and they found that although this was weakly associated with nasal–sinus disease, it was not found to be associated with olfactory function. We used rhinomanometry for nasal airflow assessment and found better olfactory scores in patients with better nasal airflow but the correlation between the two was not statistically significant.

Rydzewski et al. in their study of 240 patients with verified hypersensitivity reactions of the respiratory tract found smell disorders predominantly in patients with perennial rhinitis. They found a positive correlation between eosinophil count in blood and all olfactory parameters studied, as is the case in our study but the correlation is not statistically significant. In their study they found partial nasal obstruction in 12.2–33.3% patients but found no correlation between degree of obstruction and olfactory thresholds [18], similar to our results.

In another study conducted by Guilemany et al. impact of persistent allergic rhinitis (PER) on the sense of smell was evaluated. It was found that most patients with PER presented with Self reported hyposmia (67%); which was however not the case in our study. It was also observed that smell detection, identification and forced choice test were significantly worse in PER patients [1].

Since allergic rhinitis is known to be a Th2 specific IgE dependent immune response and IL-5 is said to play a pivotal role in tissue eosinophilia we measured levels of IgE and IL-5 in nasal secretions and found them to be elevated in allergic rhinitis patients. Kramer MF et al. in their study also found significantly higher concentrations of Interleukin-5 and Immunoglobulin E in nasal secretions. In

Table 2 Correlation of olfactory score with other variables in cases

	Olfactory score	Nasal airflow (r value)*	Peripheral eosinophilia (ρ value)	Nasal IgE (ρ value)	Nasal IL-5 (ρ value)
Correlation coefficient	1.000	.043	−.188	.039	−.243
p value**		.794	.246	.811	.131

* Correlation with nasal airflow was done using Pearson's formula

** *p* value <.05 was considered significant

addition to these they found elevated levels of Eosinophilic cationic protein. They recommended that measuring cytokines in nasal secretions is a superior method of monitoring processes in nasal diseases as compared to serum [14].

Previous studies have shown a better correlaton between inflammation and olfactory dysfunction than nasal obstruction and hyposmia. Klimek and Eggers [19] in their study demonstrated a significantly better olfactory threshold and olfactory identification testing correlation with Eosinophilic cationic protein levels than that with nasal volume flow. Cowart et al. [20] also reported that nasal obstruction did not correlate with hyposmia in patients of allergic rhinitis.

In a study conducted by Becker et al. it was concluded that olfactory dysfunction in AR patients can be ascribed to an increase in eosinophilic and mast cell activity in olfactory cleft. Therefore the decrease in olfactory functions seems to be predominantly caused by the inflammation of the epithelium and not by the obstruction of the nose caused by the inflammation [21].

Inflammatory mediators released by lymphocytes and macrophages are known to trigger hypersecretion in respiratory and Bowman's glands. Hypersecretion of olfactory mucus can lead to alteration in ion concentration, affecting the microenvironment of olfactory neurons and the transduction process.

NO has been proposed to have bronchodilator, vasodilator, neurotransmitter, mucociliary regulating and proinflammatory actions. Nasal nitric oxide, which is easily measured, provides a valuable non-invasive objective measure of the response of chronic rhinosinusitis to therapy [22].

Fractional exhaled nitric oxide (FeNO) is a non-invasive marker of airway inflammation. In a study done by Kumar et al. [23], forty-nine participants aged between 8 and 50 years were studied and 31 of them were found to be atopic. The FeNO levels in all patients ranged from 3 to 107 ppb. The mean level of FeNO in atopic group was 34.2 ± 24.3 ppb and in non-atopic group was 11.9 ± 9.0 ppb. The difference was significant ($p < .005$) [15]. In our study, FENO could be performed in 28 cases positive for SPT, out of which only 8 showed elevated levels. The mean FENO score of 28 patients was 16.854 ppb $\pm$ 13.09. On correlation with the olfactory score in cases, no significant correlation was seen amongst the two variables ($\rho = .003$, $p = .989$).

Our results show that allergic rhinitis has a moderate impact on the sense of smell. In our group of patients the olfactory score was less than that in controls reflecting the decrease in olfaction abilities. Though the inflammatory markers, namely local IgE and IL-5 were elevated in cases it did not correlate with the decrease in olfactory score ($p = .811$ and $p = .131$ respectively). The olfactory score was better in patients with a better nasal airflow, but the association was not statistically significant ($p = .794$). The reviewed literature also brings out evidence in favour of both inflammation and nasal obstruction as contributing factors to olfactory impairment in allergic rhinitis.

We concluded therefore that perhaps the mechanism of olfactory dysfunction in allergic rhinitis is a combination of decreased nasal airflow due to nasal congestion and the inflammatory environment caused due to release of inflammatory mediators. Further correlation with severity and duration of the disease is recommended.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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