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Predictors of Olfactory Dysfunction in Patients with Chronic Rhinosinusitis

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Abstract

Objectives—To measure the prevalence of and identify clinical characteristics associated with poor olfactory function in a large cohort of patients with chronic rhinosinusitis (CRS).

Study Design—Multi-institutional, cross sectional analysis.

Methods—An objective measure of olfactory dysfunction, the Smell Identification Test (SIT), demographic data, clinical factors and co-morbidity data were collected from a cohort of 367 patients who presented with CRS at three tertiary care centers. Data was analyzed using univariate and multivariate analyses.

Results—Sixty-four percent of men and women aged 18 to 64 had olfactory dysfunction whereas 95% of patients ≥ 65 years had olfactory dysfunction ($p < 0.001$); no significant difference was noted by gender. By multivariate logistic regression analysis, patients with nasal polyposis (OR 2.4, 95% confidence interval (CI) 1.3, 4.2; $p = 0.003$) and patients ≥ 65 years (OR 10.0, 95% CI 2.3, 43.7; $p = 0.002$) were at increased risk of hyposmia. Patients with nasal polyposis (OR 13.2, 95% CI 5.7, 30.7; $p < 0.001$), asthma (OR 4.2, 95% CI 1.8, 9.8; $p = 0.001$), ≥ 65 years (OR 15.6, 95% CI 2.3, 104.9; $p = 0.005$), and smokers (OR 7.6, 95% CI 1.8, 31.6; $p = 0.005$) were at increased risk of anosmia.

Conclusions—Poor olfactory function is common in patients with CRS. Age, nasal polyposis, smoking, and asthma were significantly associated with olfactory dysfunction in patients with CRS. Neither prior endoscopic sinus surgery nor a history of allergic rhinitis was associated with olfactory dysfunction. Septal deviation and inferior turbinate hypertrophy were associated with normal olfactory function.

Keywords

predictors; chronic rhinosinusitis; olfactory dysfunction; anosmia; hyposmia

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common cause of olfactory dysfunction accounting for 14–30% of cases and affecting more than 10 million people.^{1–3} The etiology of olfactory dysfunction in CRS is not well understood but appears to be multifactorial and involve both

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conductive and sensorineural mechanisms.³ Mechanical obstruction by nasal polyposis and respiratory mucosal edema can lead to decreased airflow to the olfactory cleft and a conductive disorder. Direct inflammation of the olfactory neuroepithelium in histopathology studies and clinical response to systemic corticosteroids support a sensorineural component to the disorder.^{4,5}

Despite extensive advances in the understanding of the basic science of olfaction, advances in the management of clinical olfactory dysfunction have been limited.⁶ Some clinical factors, age, gender, exposure to toxic agents, various disease states and smoking, have been extensively studied and shown to be associated with olfactory dysfunction.⁷⁻⁹ However, the role of common comorbidities in the relationship between olfactory function and CRS has not been well studied. Nasal polyposis, allergic rhinitis, asthma, septal deviation, inferior turbinate hypertrophy have been proposed to cause olfactory dysfunction, but the data is conflicting.^{7, 10-13} Prior sinus surgery has also been reported as a cause of olfactory dysfunction.¹² Furthermore, the olfactory outcomes after medical and surgical treatment for CRS have been mixed.⁷

In this large, multi-institutional cross-sectional analysis, we examine the prevalence of and clinical characteristics associated with poor olfactory function in patients with CRS. We hypothesize that age, gender, nasal polyposis, asthma, and smoking predict poor olfactory function whereas a history of sinus surgery and/or a history of allergic rhinitis do not. In turn, findings from this study may help to inform clinicians which patients are at highest risk for olfactory dysfunction and in need of patient safety counseling as well as further treatment.

MATERIALS AND METHODS

Study Population and Data Collection

Study subjects were recruited from three tertiary care centers over a three-year period (n=396). All patients had a diagnosis of CRS based on the Rhinosinusitis Task Force criteria and endorsed by the American Academy of Otolaryngology — Head and Neck Surgery.¹⁴ Adult (≥ 18 yrs old) patients were enrolled at the time they had failed maximum medical management and had elected to undergo sinus surgery. Subjects completed a medical history intake form and underwent a physical exam. Demographic and comorbidity data were documented by the physician during the interview and confirmed by physical exam and nasal endoscopy where appropriate. Variables included: age, gender, current tobacco use, prior sinus surgery, nasal polyposis, asthma, allergic rhinitis confirmed by allergy testing, acetylsalicylic acid (ASA) intolerance, septal deviation and inferior turbinate hypertrophy. Allergy testing was dependent on the clinical circumstances and may have included skin prick testing, modified radioallergic sorbent system (mRAST), or both. Patients < 18 years old, with immunodeficiency (n=5), autoimmune disease (n=8), and/or cystic fibrosis (n=12) were excluded from the study. Patients with olfactory test scores consistent with malingering (score ≤ 5) (n=4) were also excluded. A total of 367 patients (93%) were available for analysis. All study protocols and informed consent were collected and approved by Institutional Review Boards at each study site. All data was collected prospectively.

Measurement of Olfactory Function

The Smell Identification Test (SIT) from Sensonics, Inc., an objective measure of olfactory dysfunction with robust age and gender-specific normative data, was administered to patients by a trained research coordinator.¹⁵ The SIT is a validated 40 question forced-choice test (total score: 0-40). It has high test-retest reliability ($r > 0.90$) and is highly correlated with more sophisticated measures of olfactory dysfunction ($r > 0.80$).¹⁶⁻¹⁸ Absolute SIT scores are categorized into olfactory severity categories based on gender-specific normative data.¹⁵ Men

with SIT scores ranging from 34-40 and women with SIT scores ranging from 35-40 are categorized as normosmic. Men with SIT scores ranging from 19-33 and women with SIT scores ranging from 19-34 are categorized as microsmic or hyposmic. Men and women with SIT scores ranging from 6-18 are categorized as anosmic. SIT scores ranging from 0-5 are consistent with malingering. SIT scores also vary with age; however, age is not incorporated into the olfactory severity classification system. To account for this, age was included as a covariate and adjusted for in the analysis.

Statistical Analyses

Analyses were conducted using SPSS v15.0 statistical software (SPSS Inc., Chicago, IL). Demographic and clinical characteristics of study subjects were analyzed by olfactory severity category. The prevalence of normosmia, hyposmia, and anosmia was calculated for age groups (18-39 years, 40-64 years, 65+ years). Differences across the three olfactory categories by age grouping were assessed using the Jonckheere-Terpstra test for doubly ordered categories.¹⁹ Differences in the demographic data and clinical characteristics were assessed across the three olfactory severity categories. A one-way analysis of variance (ANOVA) was used to determine differences in the mean ages for the three olfactory categories. The Kruskal-Wallis test for ordered categories was used to determine differences across the olfactory categories for gender and clinical characteristics.²⁰

Two multivariate logistic regression models were constructed to examine the relationship between clinical characteristics of patients with CRS and olfactory dysfunction. The first model examined which variables were associated with hyposmia and the second model examined which variables were associated with anosmia. Age was dichotomized into two groups. This decision was made based on inspection of normative data which showed that the median SIT score for patients remained stable across early and middle adulthood and then dropped precipitously in late adulthood.¹⁵ The variable was divided into patients aged ≥ 65 years old and patients aged < 65 years old to account for this curvilinear relationship between age and normative olfactory data. All other independent variables were also dichotomized. Preliminary multilogistic regression models were constructed to include variables with univariate significance at $p < 0.25$ level. Final models were selected using forward selection ($p < 0.05$) and backwards elimination ($p > 0.10$) procedures in a stepwise fashion. Clinical factors known to predict olfactory dysfunction, such as age, gender, and smoking, and other clinical factors that were hypothesized to cause olfactory dysfunction, such as allergic rhinitis and turbinate hypertrophy, were forced into the model, but allowed to fall out if they did not remain significant. Odds ratios and 95% confidence intervals were reported. A linear regression model with the absolute SIT score as the dependent variable was also examined with similar results.

RESULTS

Thirty-three percent of patients presented with normosmia ($n=122$), 45% with hyposmia ($n=166$), and 22% with anosmia ($n=79$). The demographic and clinical characteristics of normosmic, hyposmic, and anosmic patients are described in Table I. The mean age of patients with normosmia was 43.8 years ($\pm$ standard deviation (SD) 12.5) whereas it was significantly older in hyposmic (49.8 years ($\pm$ SD 13.6)) and anosmic (49.4 yrs ($\pm$ SD 13.8) patients ($p<0.001$). Nasal polyposis, asthma, and aspirin intolerance were more common in patients with olfactory dysfunction (all $p<0.001$). Olfactory dysfunction was also more common in patients undergoing revision surgery ($p=0.026$). Septal deviation was more common in patients with normal olfactory function or less severe dysfunction ($p<0.001$); turbinate hypertrophy trended in a similar direction although this did not meet statistical significance ($p=0.077$). There were no statistically significant differences in gender, ethnicity, the proportion of smokers or the proportion of allergic patients by group.

The prevalence of hyposmia and anosmia by age and gender are illustrated in Figure I and Figure II. The proportion of patients with olfactory dysfunction was similar between the ages of 18-39 years and 40-64 years for men (60.5% vs 65.6%, $p=0.550$) and women (62.7% vs 64.1%, $p=0.860$). Ninety-five percent of men and women greater than or equal to 65 years old had olfactory dysfunction; this was significantly greater than patients under 65 years old ($p=0.008$ and $p=0.007$, respectively).

Patients with nasal polyposis (OR 2.38, 95% CI: 1.34, 4.23, $p=0.003$) and age ≥ 65 years (OR 10.0, 95% CI: 2.30, 43.71, $p=0.002$) were at significantly increased odds of hyposmia as compared to patients < 65 years old and non-polyp patients (Table II). Patients aged 65 years or greater (OR 15.59, 95% CI: 2.32, 104.86, $p=0.005$), with nasal polyposis (OR 13.21, 95% CI: 5.68, 30.70, $p<0.001$), asthma (OR 4.21, 95% CI: 1.81, 9.81, $p=0.001$), and/or current smokers (OR 7.58, 95% CI: 1.82, 31.55, $p=0.005$) were at increased odds of anosmia as compared to patients under 65 years, without nasal polyposis, non-asthmatics and non-smokers (Table II). Patients with inferior turbinate hypertrophy (OR 0.10, 95% CI: 0.01, 0.91, $p=0.041$) and/or septal deviation (OR 0.19, 95% CI: 0.06, 0.60, $p=0.005$) were less likely to have anosmia. Patients who had ASA intolerance, allergic rhinitis and/or prior sinus surgery were at neither increased nor decreased risk of olfactory dysfunction.

DISCUSSION

Clinical characteristics associated with olfactory dysfunction were examined at the time patients with CRS enrolled in a large multi-institutional, prospective cohort study. Two logistic regression models were designed to look at clinical predictors of hyposmia and anosmia as compared to patients with normosmia. We found that age ≥ 65 years, nasal polyposis, asthma, and smoking were associated with olfactory dysfunction in patients with CRS. Interestingly, when these variables were accounted for in multivariate logistic regression modeling, aspirin intolerance, allergic rhinitis, and history of prior sinus surgery were not significantly associated with olfactory dysfunction. Gender was adjusted for in the SIT scoring system based on normative data and did not require further adjustment as an independent variable in the model. Furthermore, there was no evidence of an interaction, or effect modification, between gender and CRS. Additionally, patients with septal deviation and inferior turbinate hypertrophy were less likely to have olfactory dysfunction than other patients with CRS.

Both linear and logistic regression models were examined with similar results. By reporting the results in terms of the logistic regression models, we were able to translate the associations between clinical indicators and olfactory dysfunction into quantifiable entities. Additionally, it allowed us to adjust for the nonlinear relationship between age and olfactory dysfunction.

As evident in this study and in the literature, the relationship between CRS and olfactory dysfunction appears to be multifactorial and complex. Traditionally, CRS was thought to be primarily a conductive disorder that caused mechanical obstruction of the olfactory cleft from physical obstruction of the nasal airways, nasal polyposis, edema, and secretions. However, causes other than nasal airflow appear to contribute to olfactory dysfunction.⁷ Kern noted that patients with CRS have evidence of direct inflammation of the neuroepithelium and that the degree of inflammatory changes in the neuroepithelium was related to the severity of olfactory dysfunction.⁵ This, as well as partial responses to systemic corticosteroids, has led to a better understanding that olfactory dysfunction by CRS is both a conductive and sensorineural process. Despite extensive knowledge regarding the underlying mechanisms of olfactory dysfunction, advances in the management of clinical olfactory dysfunction have been limited and treatment with oral steroids and surgery have demonstrated mixed results.

Several clinical cofactors were noted to impact the relationship between CRS and olfactory dysfunction, including age ≥ 65 years, nasal polyposis, asthma and smoking. Age is a known risk factor for olfactory dysfunction.⁹ There is increased pro-apoptotic gene expression in the olfactory mucosa of older rats and increased olfactory receptor neuron cell death.²¹⁻²² Additionally, patients with CRS and anosmia manifest moderate to severe inflammatory changes in the olfactory mucosa; inflammation, in turn, may inhibit olfactory neurogenesis.⁵ Consequently, one wonders if CRS and age may have a synergistic effect on fragile neuroepithelium in a “two-hit” fashion where older patients are more susceptible to olfactory neuroepithelial injury and less able to recover from injury.

Smoking was also associated with olfactory loss. Other studies have shown that olfactory function is inversely related to cumulative dose of smoking as well as time since last cigarette.⁸ Frye, et al showed that current smokers are 1.9 times (95% CI: 1.0, 3.8) as likely to have olfactory dysfunction as never smokers. The magnitude of this effect is relatively modest in that a four-point difference in SIT scores is noted between the highest and lowest risk groups. We found that current smokers are more likely to be anosmic than nonsmokers. As we did not measure quantity of cigarettes or time since last cigarette, we may have biased our results towards the null hypothesis.

In our model, nasal polyposis was associated with hyposmia and anosmia. Patients with nasal polyposis may suffer from a conductive olfactory loss caused by physical obstruction of the airway; they may also experience degenerative changes associated with recurrent infections, scarring, and chronic nasal medication use from long-standing polyposis.²³ Our findings are consistent with other studies.²³⁻²⁵ Perry et al reported that patients with CRS and comorbid nasal polyposis had higher subjective olfactory dysfunction scores than non-polyp patients.²⁴ Vento found that 46% of patients with long-standing nasal polyposis had elevated olfactory thresholds above the upper limit of the 95% confidence interval for a similar aged reference group.²³ A population-based study of 1387 Swedish adults found that individuals with nasal polyposis were at increased odds of olfactory dysfunction (OR 2.1, 95% CI: 1.0, 4.3) and anosmia (OR 3.8, 95% CI: 1.6, 8.8) after adjustment for other clinical characteristics, including age and gender.²⁵

In this study, patients with comorbid asthma were more likely to have olfactory dysfunction. Patients with CRS and asthma suffer from systemic inflammatory responses of the upper as well as the lower airway.²⁶ It appears that this systemic inflammatory process may affect the olfactory cleft as well. Our findings are consistent with subjective reports that olfactory dysfunction is a common complaint in patients with CRS and comorbid asthma.^{24,27}

In contrast, allergic rhinitis was not associated with olfactory dysfunction in our patient population. Allergic rhinitis often manifests itself in high flow areas of the nasal airway, such as the inferior turbinate and middle meatus, where exposure to environmental toxins is maximized; our findings suggest that lower flow areas, such as the olfactory cleft, are less affected. Apter, et al has argued that patients with allergic rhinitis are at increased risk of olfactory dysfunction as a result of recurrent respiratory tract infections that lead to damage to the olfactory neuroepithelium.¹⁰ In his study, allergic rhinitis patients with co-morbid CRS or nasal polyposis had worse olfactory function than patients with allergic rhinitis alone in a Taste and Smell Clinic. However, the subset of patients who presented to an allergy clinic for issues unrelated to olfactory complaints had normosmic olfactory thresholds. Our results are consistent with Simola, et al who found that nonallergic rhinitis patients had a poorer sense of smell than patients with seasonal or perennial allergic rhinitis.¹¹

A history of prior sinus surgery was not associated with olfactory dysfunction. Several mechanisms have been proposed to cause olfactory injury after sinonasal surgery: direct injury

to the olfactory epithelium, modification of airflow, effects of pharmacologic agents, scarring, and/or vascular injury and ischemia.^{12,28} A 1% risk of anosmia following nasal surgery has been reported.¹² However, we found that patients who had previously undergone ESS were not at increased risk for olfactory dysfunction compared to patients who had no history of sinus surgery. This is particularly interesting because according to the descriptive data, a higher proportion of patients with a history of ESS had olfactory dysfunction. However, when other variables were adjusted for in the multivariate logistic regression model, it became evident that these other variables, namely age, nasal polyposis, asthma, smoking, not a history of prior surgery, accounted for olfactory dysfunction. A previous study noted that a history of surgery for nasal polyposis was associated with poor olfactory function but a history of surgery for chronic maxillary sinusitis was not.¹¹ We suspect that it was the underlying medical comorbidity, nasal polyposis, that contributed to the olfactory dysfunction rather than the surgery. By accounting for both variables, nasal polyposis and prior sinus surgery, in our multivariate logistic regression model, we found that it was the presence of nasal polyposis not the history of prior surgery that was associated with olfactory dysfunction. Consistent with our findings, Vento et al also noted that there was no relationship between number of surgeries and olfactory threshold in patients with nasal polyposis.²³

Olfactory dysfunction is common in aspirin intolerant patients. The mean SIT score in aspirin intolerant patients was 20.7 ($\pm$ SD 10.9), but the variable was not significant in the logistic regression model. We suspect this is a limitation of the data. The power to analyze the variable may be limited by the relatively small number of aspirin intolerant patients in the study. Furthermore, both asthma and nasal polyposis were adjusted for in the model and there may be an aspect of colinearity that makes aspirin intolerance difficult to analyze. In our clinical experience, patients with aspirin intolerance frequently suffer from olfactory dysfunction although we were unable to detect it.

Septal deviation and inferior turbinate hypertrophy have been hypothesized to cause olfactory dysfunction via physical obstruction of the nasal airway.¹³ In this cohort of patients with CRS, septal deviation and inferior turbinate hypertrophy were negatively associated with olfactory dysfunction. As both diagnoses were determined by the clinician, they are subjective in nature and susceptible to potential bias. Similar to this study, Kimmelman et al found that patients undergoing septoplasty had normal preoperative SIT scores (mean SIT score 34.0) as compared to patients undergoing ethmoidectomy (mean SIT score 21.8) or polypectomy (mean SIT score 17.1).¹² Studies have shown mixed results regarding olfactory function after surgical treatment of nasal obstruction caused by septal deviation and/or inferior turbinate hypertrophy. In Kimmelman's study, there was no statistically significant difference in post-operative mean SIT scores of patients undergoing septoplasty, although one patient became anosmic.¹² In contrast, Damm et al showed that the majority of patients reported improved odor identification (80%) and odor discrimination (70%).¹³ Surgical treatment of septal deviation and/or inferior turbinate hypertrophy may alleviate nasal obstruction in this population but the impact on olfactory function is less evident. Future data collection on our patients post-operatively will help to further delineate this relationship.

CONCLUSION

Olfactory dysfunction is common in patients with CRS. Age, nasal polyposis, smoking status, and asthma are significant predictors of olfactory dysfunction. Neither a history of prior endoscopic sinus surgery nor a history of allergic rhinitis is associated with olfactory dysfunction. Septal deviation and inferior turbinate hypertrophy are associated with normal olfactory function. These findings may help to illuminate areas for future research to better understand the underlying mechanisms of olfactory dysfunction in patients with CRS.

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FIGURE I.

Prevalence of olfactory dysfunction for men across age categories: 18-39, 40-64, and 65+. The prevalence of hyposmia and anosmia in men with chronic rhinosinusitis was significantly higher in patients > 65 years old.

FIGURE II.

Prevalence of olfactory dysfunction for women across age categories: 18-39, 40-64, and 65+. The prevalence of hyposmia and anosmia in women with chronic rhinosinusitis was significantly higher in patients ≥ 65 years old.

Table I

Comparison of demographic and clinical characteristics of normosmic, hyposmic, and anosmic patients.

	Normosmic (N=122)	Hyposmic (N=166)	Anosmic (N=79)	P value
Age	43.8 +/- 12.5	49.8 +/- 13.6	49.4 +/- 13.8	<0.001
Gender				
Male	50% (61)	48.8% (81)	55.7% (44)	0.590
Female	50% (61)	51.2% (85)	44.3% (35)	
Clinical characteristics				
Nasal polyposis	18.0% (22)	33.7% (56)	74.7% (59)	<0.001
Asthma	29.5% (36)	33.1% (55)	69.6% (55)	<0.001
Aspirin Intolerance	4.1% (5)	7.2% (12)	24.1% (19)	<0.001
Allergic rhinitis	34.4% (42)	33.1% (55)	26.6% (21)	0.476
Septal deviation	31.1% (38)	28.3 (47)	7.6% (6)	<0.001
Turbinate hypertrophy	11.5% (14)	7.2% (14)	2.5% (2)	0.077
Prior sinus surgery	46.7% (57)	56.5% (94)	65.8% (52)	0.026
Smoker	5.7% (7)	8.4% (14)	7.6% (6)	0.684

Table II

Odds ratios, 95% confidence intervals (CI), and P values for each variable in the hyposmia and anosmia models.

Model	Variable	Odds Ratio (OR)	95% C.I.	P Value
Hyposmia	Age $\geq$ 65	10.03	2.30, 43.71	0.002
	Nasal polyposis	2.38	1.34, 4.23	0.003
Anosmia	Age $\geq$ 65	15.59	2.32, 104.86	0.005
	Nasal polyposis	13.21	5.68, 30.70	<0.001
	Current smoker	7.58	1.82, 31.55	0.005
	Asthma	4.21	1.81, 9.81	0.001
	Inferior turbinate hypertrophy	0.10	0.01, 0.91	0.041
	Septal deviation	0.19	0.06, 0.60	0.005