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Prevalence of allergic rhinitis and asthma in patients with chronic rhinosinusitis and gastroesophageal reflux disease

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Abstract

Background—An association between chronic rhinosinusitis (CRS) and gastroesophageal reflux disease (GERD) has been previously reported; however, the underlying factors linking CRS and GERD remain to be elucidated.

Objective—To assess the association of GERD and CRS using prospective and retrospective approaches.

Methods—The retrospective study comprised a large cohort of CRS cases, whereas the prospective arm evaluated a series of CRS cases and controls.

Results—In the retrospective arm of the study, of the 1066 patients with CRS, 112 (10.5%) had GERD. Among patients with CRS, GERD was associated with higher body mass index, older age, and female sex. The odds ratios (ORs) for asthma and allergic rhinitis in the CRS group with GERD compared with the CRS group without GERD were 2.89 (95% confidence interval [CI], 1.905–4.389) and 2.021 (95% CI, 1.035–3.947). Furthermore, GERD was associated with a greater duration of CRS. Ninety patients with CRS and 81 controls were enrolled in the prospective arm of the study. In the CRS group, GERD was associated with asthma (OR, 4.77; 95% CI, 1.27–18.01). Patients with CRS and GERD had a longer duration and a younger age at

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Supplementary Data

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onset of CRS. In controls, no association was found between GERD and asthma (OR, 0.67; 95% CI, 0.09–5.19) or allergic rhinitis (OR, 0.35; 95% CI, 0.05–2.59).

Conclusion—Patients with CRS and GERD are more likely to have atopic conditions and asthma when compared with patients with CRS but without GERD. One of the potential explanations of this link is that comorbid GERD and atopic disease are potential risk factors for development of CRS.

Introduction

Chronic rhinosinusitis (CRS) is a common disorder characterized by inflammation of the mucosal membranes of the nose and paranasal sinuses.^{1,2} Patients with CRS are typically classified into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSSNP).^{2,3} Gastroesophageal reflux disease (GERD) is a common gastrointestinal disorder that affects approximately 10% of western populations.⁴ CRS, especially refractory disease that does not improve with medical therapy, has been associated with increased risk of GERD.^{5–8} In addition, GERD is a predictor of poor symptomatic outcomes in CRS.⁹ On the other hand, Bohnhorst et al¹⁰ reported that 20.7% of patients with GERD fulfill the diagnostic criteria for CRS. This rate was significantly higher than the 8.7% CRS rate in their control group.¹⁰ In a large Veterans Affairs–based multicenter study, the odds ratio (OR) for sinusitis in patients with severe GERD compared with controls was 1.60.¹¹ GERD shares several similarities with the pathophysiology of CRS and atopy. CRS, especially CRSwNP, and GERD both can present with local infiltration of eosinophils.^{3,12–14} Furthermore, proinflammatory cytokines and eotaxins are highly expressed in both GERD and CRS.^{14–16} Despite these observations, the pathophysiologic links between GERD and CRS remain to be clarified. Moreover, the association of GERD with CRS phenotypes has not been previously evaluated. A careful analysis of these associations is an important step in providing clues about the underlying pathophysiologic mechanism of this association. This may facilitate identification of methods and strategies for early diagnosis or prevention of disease and decreasing its burden. In this study, we aimed to explore the association of CRS and GERD and to investigate factors associated with GERD and CRS in a well-defined large study.

Methods

Patients

This study was approved by the Rush University Medical Center Institutional Review Board. A large study with retrospective and prospective arms was performed to study the association of CRS with GERD. All patients in the prospective arm provided signed informed consent. CRS was diagnosed based on guidelines of the American Academy of Otolaryngology–Head and Neck Surgery Chronic Rhinosinusitis Task Force.¹⁷ All cases needed to have documented continuous rhinosinusitis symptoms for at least 12 weeks with objective findings on sinus computed tomography or endoscopic evaluation to be included in the study. The diagnosis of GERD was based on positive symptoms of heartburn and regurgitation clearly documented in the medical record plus response to empiric therapy with proton pump inhibitors (PPIs) or histamine₂-receptor antagonists based on the

American College of Gastroenterology guidelines for the diagnosis and management of GERD.^{18,19} The medical records of all patients with CRS in our previously reported large CRS cohort²⁰ were reviewed to extract clinical information about the diagnosis of GERD. Cases with possible diagnosis without evidence of treatment were excluded. On the basis of these guidelines, we focused on heartburn and regurgitation for inclusion, and any patients with extra esophageal symptoms (chronic cough, globus sensation, and dysphonia) without heartburn or regurgitation were excluded from the study.

In the prospective study, a group of patients with CRS treated in the allergy or otolaryngology clinics were recruited. A group of age-, sex-, and body mass index (BMI)-matched controls visiting the same clinics were recruited as control subjects. These CRS cases and controls were asked to complete a questionnaire about GERD symptoms and treatment followed by detailed review of their electronic medical records.

We used a standard questionnaire, the sino-nasal outcome test (SNOT-22), which is a scoring system based on severity of symptoms and the social and emotional consequences of CRS and is the most accepted patient-reported outcome measure in CRS.^{21,22} The questionnaire was offered to the CRS case patients in the prospective series.

Covariates

Three main categories of variables were analyzed in association with the presence of GERD in this series: (1) demographic risk factors (age, sex, race, and BMI [calculated as weight in kilograms divided by the square of height in meters]), (2) comorbid conditions (asthma, allergic rhinitis, eczema, and aspirin-exacerbated respiratory disease), and (3) factors pertaining to the severity of CRS. The variables are defined in eTable 1.

Statistical Analysis

The unadjusted comparisons between patients with CRS and control patients enrolled in the prospective arm were made by χ^2 or *t* test as appropriate. In the retrospective and prospective series of CRS, patients were grouped as CRS with GERD or CRS without GERD. Logistic regression was used to adjust for covariates associated with GERD in CRS. All analyses were adjusted for age, sex, and BMI. Data are presented as ORs and 95% confidence intervals (CIs) or regression coefficient of each variable in CRS with GERD compared with CRS without GERD. SPSS statistical software, version 21 (SPSS Inc, Chicago, Illinois), was used for statistical analyses. Differences were considered statistically significant at $P < .05$.

Results

Retrospective Arm

The retrospective cohort included 1066 patients with documented diagnosis of CRS. A total of 112 cases (10.5%) had GERD based on the aforementioned criteria. Eighty-four patients with a possible GERD diagnosis without documented treatment did not fulfill the criteria and were excluded from the study.

The mean BMI of the CRS with GERD group was higher compared with the CRS without GERD group (30.78 vs 28.68, $P < .05$). The CRS with GERD group also had a higher mean age (54.67 vs 49.59 years, $P < .05$). GERD was more prevalent in Asian individuals (28.6%) compared with white, Latino, and African American individuals at 10.0%, 5.8%, and 14.5%, respectively ($P < .05$). A higher proportion of the CRS with GERD group was female compared with the CRS without GERD group (68.8% vs 58.8%, $P < .05$). Next, a logistic regression analysis model adjusting for age, sex, and BMI was applied to test the association of multiple variables with GERD in CRS. The patients with CRS and GERD were more likely to have asthma compared with the patients with CRS without GERD, whereas GERD in the patients with CRS was not associated with eczema and aspirin-exacerbated respiratory disease (Table 1). Among the patients who have been evaluated for allergic rhinitis by serum specific IgE measurement and/or skin prick test to a standard panel of aeroallergens detailed in eTable 1 (368 cases), allergic rhinitis was associated with GERD. Of note, there was no statistical difference between GERD and non-GERD cases in terms of evaluation for allergic rhinitis.

The number of operations for CRS was not associated with GERD. However, the duration of CRS was longer in CRS with GERD cases (13.4 vs 9.4 years, $P < .05$). No significant difference was found in the prevalence of GERD between CRSsNP (33.0%) and CRSwNP (33.2%) forms of CRS disease ($P = .89$).

Prospective Arm

The prospective arm included 90 patients with CRS and 82 patients in the control group. The demographics and patient characteristics are detailed in Table 2. Patients with CRS had a higher prevalence of GERD compared with controls (15.6% vs 7.4%, $P = .07$). Similar to the retrospective series, GERD was significantly associated with higher BMI in both cases and controls. Consistent with the retrospective arm, GERD was associated with asthma in the CRS group. Furthermore, patients with CRS and GERD had a higher prevalence of allergic rhinitis (OR, 3.19; 95% CI, 0.84–12.13) which was close to being significant ($P = .07$). Similar to the retrospective arm, patients with CRS and GERD had a longer duration of CRS compared with patients with CRS without GERD, with a mean of 19.9 vs 10.9 years. In addition, patients with CRS and GERD had a significantly earlier age at onset of CRS compared with patients with CRS without GERD (Table 3). In controls, atopic disease was not associated with GERD. The ORs of asthma, atopy, and eczema in GERD control cases compared with non-GERD control cases were 0.67 (95% CI, 0.09–5.19), 0.35 (95% CI, 0.05–2.59), and 0.22 (95% CI, 0.02–2.65), respectively.

Effect of GERD on Sinonasal Symptoms in CRS

From our prospective series, 75 patients completed a standard validated questionnaire called SNOT-22 to evaluate the severity of CRS symptoms and the effect of these symptoms on patients' well-being.^{21,22} This questionnaire includes 22 questions (Table 4), and the answer to each question is based on a scale of 0 to 5, with 0 indicating no problem and 5 indicating as bad as it can be. Patients with CRS and GERD had significantly higher scores in response to questions investigating nasal symptoms: need to blow the nose, nasal blockage, runny

nose, cough, and facial pain or pressure. Furthermore, patients with CRS and GERD had a higher total SNOT-22 score (Table 4).

Discussion

Many interesting observations stem from this study. In the prospective series, there was more GERD among the patients with CRS, and comorbid CRS with GERD was significantly associated with higher BMI and female sex, which have been identified as risk factors for GERD in the general population.^{23,24} A similar association of GERD was found with BMI in the control group, but there was no association between GERD and asthma or allergic rhinitis in this group. All our analyses were corrected for demographic factors and BMI. We found for the first time that in patients with CRS, GERD has a significant association with asthma, allergic rhinitis, and longer duration of disease.

In our prospective series, we found an association between GERD and increased reported nasal symptoms, including nasal blockage, rhinorrhea, facial pressure, and cough, in the SNOT-22 questionnaire. The mechanism underlying the link between CRS and GERD is still unclear. One of the most commonly accepted hypotheses is that GERD provides a direct insult to the upper respiratory tract mucosa via reflux of gastric acid. This hypothesis was first suggested on the basis of studies reporting an association between upper respiratory tract inflammation and GERD in children.^{25–27} In one study, pH recordings in patients with refractory CRS revealed increased reflux events into the nasopharynx in CRS. These results were not reproduced by other studies in general CRS cases.^{6,8} This hypothesis could be challenged because not all patients with GERD have reflux up to the nasopharynx. The reported reflux into the nasopharynx is only seen in a subset of patients with extraesophageal reflux also known as laryngopharyngeal reflux disease. An alternative hypothesis suggests the involvement of the autonomic nervous system in CRS. Autonomic dysregulation can link GERD and CRS based on the shared parasympathetic innervation of the gastrointestinal and upper respiratory tracts.^{28,29} Infusion of hydrochloric acid and normal saline in the lower esophagus in healthy individuals leads to increased mucous secretion and nasal inspiratory peak flow, indicating a neural reflex between the esophagus and the nasal cavity.²⁹ The increased nasal symptoms in patients with CRS and GERD seen in our series is in agreement with a previous report²⁹ and has been attributed to a gastronasal reflex based on a report by Wong et al.²⁹ In their study, Wong et al found a tendency toward an increase in nasal symptoms score and nasal mucous production after infusion of hydrochloric acid or normal saline in the lower esophagus via an esophageal manometry catheter.²⁹ This finding was suggestive of a neural reflex between the nasal mucosa and the esophagus via the vagus nerve.²⁹ Interestingly, a similar effect has been seen on lung airflow in asthma. Schan et al³⁰ found that infusion of acid into the esophagus caused a decrease in peak expiratory flow in healthy controls and patients with asthma with and without GERD. Although this does not necessarily imply a causative mechanism, it certainly merits further investigation to better understand the complex associations between the 2 disease processes.

In our study, GERD was significantly associated with atopic diseases, specifically asthma and allergic rhinitis. Perhaps a mutual allergic inflammation in response to an allergen or allergens with high cross-reactivity that come in contact with both mucosal membranes

could be the drive for atopic diseases and GERD in CRS cases. One possible explanation is sensitivity and reaction to common pollen and food allergens, such as profilins and PR-10. IgE has a higher degree of cross-reactivity compared with other types of immunoglobulins,³¹ which is the basis of the high rate of cross-reactivity of certain tree or grass pollens IgE, such as Bet v 1, with different labile food allergens found in fresh fruits and vegetables.³² Sensitization to these allergens in a group of patients with allergic rhinitis is the underlying mechanism of pollen food allergy syndrome. Potentially, sensitization and reactivity to these allergens, especially to lipid transfer proteins, which are less labile and not degraded by stomach acid, can result in both allergic rhinitis through the pollen in susceptible patients and contribute to CRS, whereas exposure to lipid transfer proteins in fresh fruits results in inflammation in the upper gastrointestinal tract, resulting in GERD symptoms. Eosinophils, a key component of the pathophysiology of allergic inflammation and CRS,³³ are also found in esophageal mucosa in GERD. Recruitment and survival of eosinophils are driven and enhanced by eotaxin 3, interleukin (IL) 5, and IL-13 in the respiratory³⁴ and upper gastrointestinal tract. An acidic environment prevents apoptosis of eosinophils,³⁵ and treatment with proton pump inhibitors decreases the gene expression of IL-5 and IL-13³⁶ and blocks the expression of eotaxin 3 from esophageal epithelial cells.^{37,38} As outlined above, few studies have found evidence of gastric acid reflux up to the nasopharynx in patients with CRS and GERD.^{7,39} In the setting of GERD, an acidic environment may promote uncontrolled eosinophilic inflammation, especially in a predisposed allergic individual. Furthermore, acid can irritate and affect the integrity of epithelial barrier in the upper airways and increase mucous production,²⁹ which could potentially create the milieu for development of increased chronic inflammation in the paranasal sinuses and propagation of CRS. Along the same lines, GERD was associated with greater duration of CRS and earlier age at onset in our prospective series. This finding, along with the previous reports of a higher prevalence of CRS in GERD, indicates that GERD could be a contributing event that may promote the pathogenesis of CRS.

We found an association between Asian race and GERD in CRS in the retrospective arm of the study. Because of the lower number of cases in the prospective arm, we did not have the power to test this association. Previous reports have found a lower prevalence of GERD in Asian populations in the Far East⁴⁰ and a lower rate of GERD symptoms in Asian populations in the United States⁴¹ compared with white and Hispanic populations.⁴¹ Although Asian populations in general are less prone to GERD, this is not the case among patients with CRS, which is indicative of the strong association of these 2 conditions in this population. The CRS histopathologic mechanisms are different in Asian compared with white populations,⁴² which along with this new finding warrants more investigation.

The current report is the first large study investigating the prevalence of GERD and identifying its risk factors in a cohort of patients with CRS. Replication of the results of the retrospective series in our prospective cohort of patients with CRS confirms the validity of the findings. One limitation of this study is that the data are from a tertiary care referral center, and potentially the CRS cohort, especially the prospective series, may include a more severe phenotype of CRS. However, in the retrospective cohort, the mean number of sinus operations was less than 1, indicating that the series included a significant number of patients with milder disease. Another limitation of the study was the use of clinical diagnosis

for GERD. As detailed in the American College of Gastroenterology guidelines, the diagnosis of GERD based on clinical symptoms and response to therapy is not 100% sensitive.^{18,19} However, the goal of our study was to investigate the factors associated with GERD in CRS in the clinical setting, and currently these criteria are the recommended diagnostic tool for GERD in practice. We placed strict inclusion criteria for both diagnoses, and all these data in the retrospective arm were confirmed by 2 independent investigators. The focus of our study was on symptoms of GERD specific to the esophagus. We did not investigate the association of extra esophageal symptoms in patients with GERD and CRS because of the inconsistency in the literature regarding the workup and treatment of laryngopharyngeal or extraesophageal reflux. More detailed studies looking at the evidence for extraesophageal reflux by objective methods in atopic patients with CRS would be informative in paving the road toward understanding the mechanism of atopic airway diseases in association with reflux.

The current series found a significant association of GERD with asthma and allergic rhinitis and a greater duration of disease in patients with CRS in a large retrospective series. A significant association of GERD with asthma and a longer duration of disease, as well as a close to significant association with allergic rhinitis, were found in our prospective study. One potential explanation is that the inflammatory response, in association with GERD, could be further aggravated in the setting of preexisting eosinophilic inflammation because of atopic airway disease and play a role in the pathogenesis of CRS. GERD is a treatable condition, and proactive identification and treatment, especially in atopic patients, could have a significant role in preventing more advanced inflammatory diseases of the airways. However, this important area merits further research to investigate the mechanisms underlying the association of GERD and atopy in patients with CRS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and Clinical Characteristics of Patients With Chronic Rhinosinusitis (CRS) With Gastroesophageal Reflux Diseases (GERD) Compared With Patients With CRS Without GERD in the Retrospective Series

Characteristic	OR (95% CI) or regression coefficient (SE) in patients with GERD with CRS compared with patients with CRS without GERD ^a
Female sex	1.19 (0.83–1.71)
Age	0.18 (0.007) ^b
BMI	0.45 (0.13) ^b
Race	
White	0.428 (0.127–1.434)
African American	0.743 (0.476–1.158)
Latino	0.663 (0.124–3.438)
Asian	2.730 (1.154–6.454) ^b
Nasal polyp	0.999 (0.649–1.538)
Asthma	2.891 (1.905–4.389) ^b
AERD	1.042 (0.397–2.738)
Allergic rhinitis	2.021 (1.035–3.947) ^b
Eczema	1.397 (0.677–2.882)
No. of FESS operations	
Regression coefficient (SE)	–0.021 (0.94)
Mean (SD) (in patients with GERD with CRS vs patients with CRS without GERD)	0.69 (0.97) vs 0.71 (1.25)
Duration of disease, y	
Regression coefficient (SE)	0.30 (0.009) ^b
Mean (SD) (in patients with GERD with CRS vs patients with CRS without GERD)	13.36 (14.48) vs 9.43 (10.46)

Abbreviations: AERD, aspirin-exacerbated respiratory disease; BMI, body mass index; CI, confidence interval; CRS, chronic rhinosinusitis; FESS, functional endoscopic sinus surgery; GERD, gastroesophageal reflux disease; OR, odds ratio.

^aThe reported ORs (95% CIs) for all categorical variables and the regression coefficients (SEs) for numeric variables were calculated in patients with GERD with CRS compared with patients with CRS without GERD by regression adjusting for age, sex, and BMI.

^b $P < .05$.

Table 2

Demographic and Clinical Characteristics of 90 Patients With CRS and 81 Control Cases Without CRS:
Results of the Prospective Arm of the Study

Characteristic	CRS group (n = 90)	Control group (n = 81)	P value ^a
GERD, %	15.6%	7.4%	.07
Female sex, %	55.6%	58.0%	NS
Age, mean (SD), y	43.77	43.19	NS
BMI, mean (SD), y	29.47	27.36	NS
Race, %			
White	61.1%	59.2%	NS
African American	26.7%	19.5%	
Latino	11.1%	14.8%	
Asian	1.1%	3.7%	
Asthma, %	34.6%	36.7%	NS
AERD, %	14.5%	0	NA
Allergic rhinitis, %	38.9%	29.6%	NA
Eczema, %	15.5%	22.7%	NS

Abbreviations: AERD, aspirin-exacerbated respiratory disease; BMI, body mass index; CRS, chronic rhinosinusitis; GERD, gastroesophageal reflux disease; NA, not applicable; NS, not significant.

^aP values are calculated by the χ^2 or *t* test as appropriate comparing the variables in patients with CRS with controls.

Table 3

Clinical Characteristics of Patients With CRS With GERD Compared With Patients With CRS Without GERD: Results of the Prospective Arm of the Study

Characteristic	OR (95% CI) or regression coefficient (SE) in patients with GERD with CRS compared with patients with CRS without GERD ^a
Nasal polyp	0.71 (0.21–2.35)
Asthma	4.77 (1.27–18.01) ^b
Allergic rhinitis	3.19 (0.84–12.13)
Eczema	0.49 (0.06–4.28)
AERD	1.32 (0.30–5.66)
No. of FESS operations	
Regression coefficient (SE)	0.26 (0.16)
Mean (SD) (in patients with GERD with CRS vs patients with CRS without GERD)	3.10 (2.92) vs 1.98 (1.86)
Duration of disease, y	
Regression coefficient (SE)	0.18 (0.09) ^b
Mean (SD) (in patients with GERD with CRS vs patients with CRS without GERD)	19.9 (11.52) vs 10.92 (8.29)
Age at CRS onset, y	
Regression coefficient (SE)	–0.49 (0.24) ^b
Mean (SD) (in patients with GERD with CRS vs patients with CRS without GERD)	26.61 (13.09) vs 37.27 (16.26)

Abbreviations: AERD, aspirin-exacerbated respiratory disease; BMI, body mass index; CI, confidence interval; CRS, chronic rhinosinusitis; FESS, functional endoscopic sinus surgery; GERD, gastroesophageal reflux disease; OR, odds ratio.

^aThe reported ORs (95% CIs) for all categorical variables and the regression coefficients (SEs) for numeric variables were calculated in patients with GERD with CRS compared with patients with CRS without GERD by regression adjusting for age, sex, and BMI.

^b $P < .05$.

Table 4

Results of the SNOT-22 Questionnaire in Patients With CRS With GERD Compared With Patients With CRS Without GERD: Results of the Prospective Arm of the Study^a

SNOT-22 question	Patients with CRS without -GERD (n = 10)	Patients with CRS with GERD (n = 65)	P value (t test)
1. Need to blow nose (mean score)	2.06	3.3	.03 ^b
2. Nasal blockage	1.12	2.0	.04 ^b
3. Sneezing	1.54	2.5	.08
4. Runny nose	1.63	3.22	.01 ^b
5. Cough	2.27	4.1	.003 ^b
6. Postnasal discharge	2.16	3.09	.12
7. Thick nasal discharge	1.62	2.22	.33
8. Ear fullness	1.08	2.0	.12
9. Dizziness	0.85	1.5	.20
10. Ear pain	1.32	1.56	.68
11. Facial pain or pressure	1.45	2.9	.01 ^b
12. Decreased sense of smell or taste	1.93	2.9	.11
13. Difficulty falling asleep	2.29	3.3	.10
14. Wake up at night	2.41	2.5	.88
15. Lack of a good night's sleep	2.44	2.4	.97
16. Wake up tired	1.74	2.33	.34
17. Fatigue	1.65	1.8	.79
18. Reduced productivity	1.66	2.2	.35
19. Reduced concentration	1.18	1.4	.69
20. Frustrated, restless, or irritable	0.7	0.7	.10
21. Sad	1.81	2.9	.054
22. Embarrassed	2.56	3.5	.13
Total SNOT-22 score	35.92	52.45	.04 ^b

Abbreviations: CRS, chronic rhinosinusitis; GERD, gastroesophageal reflux disease; SNOT-22, sino-nasal outcome test.

Adapted from Piccirillo et al²¹. SNOT-22 was developed from modification of SNOT-20 by National Comparative Audit of Surgery for Nasal Polyposis and Rhinosinusitis, Royal College of Surgeons of England. SNOT-20 © 1996 by Jay F. Piccirillo, MD, Washington University School of Medicine, St. Louis, Missouri.

^aScores are based on a scale of 0 to 5 that patients have chosen in answer to each question, with 0 indicating no problem and 5 indicating problem as bad as it can be.

^b $P < .05$.