

Risk factors for development of chronic rhinosinusitis in patients with allergic rhinitis

Ahmad R. Sedaghat, MD, PhD^{1,2,3}, Stacey T. Gray, MD^{1,3}, Claus O. Wilke, PhD⁴,
David S. Caradonna, MD, DMD^{2,3}

Background: Chronic rhinosinusitis (CRS) is a heterogeneous inflammatory condition of the sinonasal cavity. CRS may be preceded by other sinonasal inflammatory diseases including allergic rhinitis (AR). It is unclear what factors may predispose patients with AR to develop CRS.

Methods: We performed a retrospective review of all patients diagnosed with AR (and not CRS) that presented to an otolaryngology clinic at a tertiary care center as part of a multidisciplinary allergy evaluation between March 2004 and November 2011. Medical records were evaluated for clinicodemographic factors including age, gender, smoking history, asthma, gastroesophageal reflux disease (GERD), aspirin sensitivity, nasal polyposis, seasonal AR, perennial AR, categories of positive antigens on formal allergy testing, and the following sinonasal anatomic variants on computed tomography (CT): infraorbital (Haller) cells, concha bullosa, frontal intersinus cells, and anterior ethmoid frontal recess cells. Patients who did not develop CRS after at least 4 years of follow-up were grouped into the AR cohort. Patients who developed CRS after at least 6 months of follow-up were grouped into the AR-CRS cohort.

Results: We found a statistically significant association between the presence of infraorbital (Haller) cells (odds ratio [OR] = 6.27) and frontal intersinus cells (OR = 18.37) with development of CRS on both univariate and multivariate logistical regressions.

Conclusion: Sinonasal anatomical variants, specifically infraorbital and frontal intersinus cells, are associated with development of CRS in patients with AR. The presence of these variants identifies patients who should be counseled on compliance with medical therapy for AR to potentially prevent progression to CRS. © 2012 ARS-AAOA, LLC.

Key Words:

allergic rhinitis; chronic rhinosinusitis; computed tomography; infraorbital cell; Haller cell; frontal intersinus cell

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Chronic rhinosinusitis (CRS) is characterized by heterogeneous, chronic inflammatory processes of the sinonasal mucosa¹ leading to symptoms of facial pain/pressure, nasal congestion, and/or purulent drainage.² With over 10 million diagnosed individuals and an esti-

mated \$8.6 billion spent annually in total health care expenditures in the United States alone, CRS is a major burden on the healthcare system.³ Currently, the initial treatment for uncomplicated CRS is conservative medical therapy, including antibiotics and corticosteroids.⁴ Surgical intervention with endoscopic sinus surgery is considered⁵ if appropriate medical therapies fail. Treatment of CRS is targeted toward long-term symptom control rather than cure, as the underlying inflammatory causes of CRS in most patients are never completely eradicated, and patients often remain on long-term maintenance therapy.⁴ Despite such poor prognosis for long-term disease-free survival, no preventative strategies exist in clinical practice because given the current data on CRS risk factors there is limited scope for identifying individuals at risk for developing the disease.

Allergic rhinitis (AR) has been reported to be associated with CRS.⁶ Although evidence for a causal relationship between AR and CRS is lacking, there are many lines of evidence through epidemiologic association⁷⁻⁹ and common cellular and molecular mediators¹ which suggest that AR

¹Department of Otolaryngology–Head and Neck Surgery, Massachusetts Eye and Ear Infirmary, Boston, MA; ²Division of Otolaryngology, Beth Israel Deaconess Medical Center, Boston, MA; ³Department of Otolaryngology and Laryngology, Harvard Medical School, Boston, MA; ⁴Section of Integrative Biology, Center for Computational Biology and Bioinformatics, and Institute for Cell and Molecular Biology, The University of Texas at Austin, Austin, TX

Correspondence to: Ahmad R. Sedaghat, MD, PhD, Department of Otolaryngology–Head and Neck Surgery, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114; e-mail: ahmad.sedaghat@meei.harvard.edu

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is an inflammatory instigator or an exacerbating factor for CRS.

We hypothesize that AR, while not necessarily a causative agent of CRS, produces a chronic, inflammatory milieu in the sinonasal mucosa, which in the right setting may predispose patients to develop CRS. We assessed 2 cohorts of patients diagnosed with AR who underwent a multidisciplinary evaluation and long-term follow-up. One cohort developed CRS during the course of follow-up and the other cohort did not develop CRS. We hypothesized that direct comparison of medical comorbidities and sinonasal anatomy in these 2 cohorts may identify clinical risk factors in patients with AR that may predispose to subsequent development of CRS.

Patients and methods

Patient selection

Approval for this study was obtained from the Beth Israel Deaconess Medical Center Institutional Review Board. A consecutive series of adult patients having only the clinically determined diagnosis of AR at initial presentation between March 2004 and November 2011 was screened. The diagnosis of AR was dependent on symptomatology and positive skin or radioallergosorbent test (RAST) testing by an allergist. Endoscopic examination of the nasal cavity was routinely performed on patients at the time of the initial presentation and diagnosis of AR. A diagnosis of CRS was made based on guideline-established criteria^{2,10} set by the American Academy of Otolaryngology–Head and Neck Surgery that are based on patient-reported history and objective findings on computed tomography (CT) scan or endoscopic examination. All patients followed for 4 or more years without meeting guideline-established criteria for diagnosis of CRS comprise the AR cohort. All patients who met criteria for diagnosis of CRS after the first 6 months of follow-up comprise the AR to CRS (AR-CRS) cohort. Clinicodemographic data collected consisted of information that is commonly collected as a part of a routine AR workup. Demographic data collected included age, gender, and current tobacco use. Clinical data recorded included history of medical comorbidities associated with CRS: asthma,^{11,12} aspirin sensitivity, nasal polyposis at the time of presentation (reflected by the Lund nasal polyp score),¹³ history of recurrent acute rhinosinusitis, and gastroesophageal reflux disease (GERD).^{14,15} Diagnoses of GERD, asthma, and aspirin sensitivity were recorded as positive based on patient history, and confirmed with supporting documentation by the patient's internal medicine physician or allergist, including prescription of appropriate medication. A patient was considered to have presented with recurrent acute rhinosinusitis if he or she had greater than 4 distinct episodes of acute sinusitis per year for at least 1 year preceding the initial presentation.^{2,10}

An allergic profile was determined as follows. History of seasonal and/or perennial allergies was recorded. More-

over, positive allergy testing for antigens categorized as: (1) a pollen; (2) dust mite; (3) cat; (4) dog; (5) fungus or mold; or (6) cockroach were noted as well. Patients with previous history of CRS, sinus surgery, or cystic fibrosis were excluded.

Image analysis

Head or sinus CT scans, when available, were evaluated, blinded to which cohort the patient belonged, for the presence of infraorbital ethmoid cells (also known as Haller cells) and concha bullosa (pneumatized middle turbinate), both of which may serve as obstructions of the osteomeatal unit (OMU) where the maxillary, anterior ethmoid, and frontal sinuses drain.^{16,17} We evaluated obstruction of the frontal recess by frontal intersinus cells and anterior ethmoid cells. A frontal intersinus cell is a distinct air cell within the intersinus septum of the frontal sinuses and has an outflow tract into either the left or right frontal recess. Frontal intersinus cells may obstruct frontal sinus outflow by impinging on the frontal recess. Anterior ethmoid cells in the frontal recess are classified according to the Kuhn classification,¹⁸ in which higher classes indicate greater encroachment into the frontal recess or frontal sinus. For our analyses, we considered the highest Kuhn class from either the patient's left or right side. Head or sinus CT scans were available in the medical record for 26 of 35 patients in the AR cohort, obtained in order to rule out CRS at the time of presentation in patients. All patients in the AR-CRS cohort had sinus CT scans performed at the time that CRS was diagnosed. Of the 24 patients in the AR-CRS cohort, 23 had available sinus CT scans in the medical record.

Statistical analysis

All analysis was performed with the R statistical software (www.r-project.org). Associations between development of CRS and predictor variables were determined with the logistic regression function `lm()` in the `rms` package.¹⁹ Univariate logistic regression was performed for each predictor variable. Multivariate logistical analysis was performed using all clinicodemographic and anatomic variables. Multivariate logistical analysis was performed separately for predictor variables of the allergy profile due to sparsity of data availability in the medical record compared to clinicodemographic and anatomic characteristics. In the multivariate model, significant predictors were identified via backward elimination, using a *p* value cutoff of 0.100. For each variable retained in the final model, a *p* value and a log-odds ratio (OR) were calculated.

Results

Characteristics of study subjects

We found 35 patients who met criteria for the AR cohort (Table 1). This cohort was 40% male and 60% female with mean $\pm$ standard deviation (SD) age of 46.4 ± 12.0 years at the initial presentation. We found 24 patients who

met criteria for the AR-CRS cohort (Table 1). The AR-CRS cohort was 41.7% male and 58.3% female with mean age of 45.7 ± 12.0 years at initial presentation. The median follow-up time for patients in the AR cohort was 5.3 (range, 4.1–9.3) years. The median time to development of CRS was 3.4 years with 75% diagnosed by 4.1 years. We found 5.7% of patients in the AR cohort reported current smoking at the time of presentation in comparison to 8.3% of patients in the AR-CRS. There was no significant difference in the average age at presentation, gender, or frequency of currently smoking patients between the 2 cohorts (Table 1).

Contribution of medical comorbidities

We evaluated the association of comorbidities GERD, asthma, aspirin sensitivity, and nasal polyposis (Table 1) with development of CRS. In the AR cohort, 40.0% of patients had GERD and 17.1% presented with a history of recurrent sinusitis. In comparison, 29.1% of patients had GERD and 12.5% had recurrent sinusitis in the AR-CRS cohort. There was no significant association between a history of GERD or recurrent sinusitis with the development of CRS (Table 1).

We found that 34.3% of patients in the AR cohort had asthma and 41.7% of patients in the AR-CRS cohort had asthma. The presence of nasal polyps was not common in either cohort, occurring in 8.7% of patients in the AR cohort (average Lund nasal polyp score of 1.7) and 8.3% in the AR-CRS cohort (average polyp score of 1.5). Although uncommon, nasal polyposis may be present in the absence of CRS (ie, nasal polyposis does not obligately lead to a diagnosis of CRS according to published guidelines^{2,10}). In the AR cohort, 1 patient was described as having a single small polyp arising from the middle meatus; the other pa-

tient had more extensive polyposis in the setting of Samter's triad, although no air-fluid level was seen on CT scan which was consistent with the lack of purulence seen on nasal endoscopy performed in the clinic. Neither asthma nor nasal polyposis significantly associated with progression to CRS (Table 1). We also considered the association of aspirin sensitivity, because Samter's triad may be associated with CRS. We found that 2.8% of patients in the AR cohort had aspirin sensitivity and 16.7% of patients in the AR-CRS cohort had aspirin sensitivity. There was a trend toward a significant association between aspirin sensitivity and development of CRS on univariate regression ($p = 0.096$) but not on multivariate ($p = 0.858$) regression.

We furthermore considered atopic characteristics as potential risk factors for development of CRS (Table 2). We found that 74.2% of AR patients had seasonal AR in comparison to 78.9% in the AR-CRS cohort. Perennial AR was present in 96.4% of the patients in the AR cohort and 89.5% of patients in the AR-CRS cohort. Neither seasonal AR nor perennial AR was associated with development of CRS (Table 2). Similarly, we did not find any statistically significant association between positive allergy testing for any antigens in the specified categories and development of CRS (Table 2).

Contribution of anatomical factors

We considered the role of obstructive sinonasal anatomic variants in the development of CRS (Table 3). In the OMU, we found that 19.2% of AR patients had a concha bullosa in comparison to 41.7% of AR-CRS patients. Association between the presence of concha bullosa and development of CRS trended toward statistical significance on univariate regression ($p = 0.090$) but not on multivariate ($p = 0.988$) regression. We did, however, find that 100% of patients in

TABLE 1. Clinicodemographic data

	AR patients, mean (SD)	AR-CRS patients, mean (SD)	Univariate p value	Univariate OR (95% CI)	Multivariate p value	Multivariate OR (95% CI)
Age ^a (years)	46.4 (12.0)	45.7 (12.0)	0.837	1.00 (0.95–1.04)	0.748	1.01 (0.94–1.09)
Gender (%)						
M	40.0 (8.3)	41.7 (10.0)	0.898	1.07 (0.37–3.08)	0.640	1.49 (0.28–8.05)
F	60.0 (8.3)	58.3 (10.0)				
Tobacco usage (%)	5.7 (3.9)	8.3 (5.6)	0.696	1.50 (0.20–11.45)	0.517	0.36 (0.02–8.12)
GERD (%)	40.0 (8.3)	29.1 (9.3)	0.395	0.62 (0.20–1.87)	0.466	0.56 (0.12–2.63)
Recurrent sinusitis (%)	17.1 (6.4)	12.5 (6.7)	0.627	0.69 (0.15–3.08)	0.376	0.40 (0.05–3.00)
Asthma (%)	34.3 (8.0)	41.7 (10.1)	0.565	1.37 (0.47–3.99)	0.348	2.13 (0.44–10.33)
ASA sensitivity (%)	2.8 (2.8)	16.7 (7.6)	0.096	6.80 (0.71–65.16)	0.858	1.03 (0.03–31.29)
Nasal polyps			0.894	0.93 (0.33–2.66)	0.473	0.58 (0.16–2.07)
Prevalence (%)	8.7 (4.7)	8.3 (5.6)				
Score	1.7	1.5				

^aAge at initial presentation and diagnosis of AR.

AR = allergic rhinitis; ASA = aspirin; CI = confidence interval; CRS = chronic rhinosinusitis; F = female; GERD = gastrointestinal reflux disease; M = male; OR = odds ratio; SD = standard deviation.

TABLE 2. AR profile

	AR Patients, mean (SD)	AR-CRS patients, mean (SD)	Univariate <i>p</i> value	Univariate OR (95% CI)	Multivariate <i>p</i> value	Multivariate OR (95% CI)
Seasonal AR (%)	74.2 (7.9)	78.9 (9.4)	0.702	1.30 (0.33–5.11)	0.965	0.92 (0.03–31.01)
Perennial AR (%)	96.4 (3.5)	89.5 (7.0)	0.360	0.31 (0.03–3.74)	0.479	0.33 (0.02–7.09)
Allergen profile (%)						
Pollens	71.4 (8.5)	80.0 (10.3)	0.541	1.60 (0.35–7.23)	0.758	0.74 (0.10–5.16)
Dust mite	74.1 (8.4)	68.8 (11.6)	0.707	0.77 (0.20–3.01)	0.833	1.20 (0.21–6.83)
Cat	55.6 (9.6)	40.0 (12.6)	0.337	0.75 (0.21–2.70)	0.119	0.17 (0.01–3.28)
Dog	25.9 (8.4)	28.6 (12.1)	0.856	1.14 (0.27–4.84)	0.271	4.57 (0.40–51.14)
Fungus/mold	25.9 (8.4)	35.7 (12.8)	0.515	1.59 (0.39–6.38)	0.418	1.84 (0.42–8.11)
Cockroach	11.1 (6.0)	21.4 (11.0)	0.383	2.18 (0.38–12.58)	0.2306	2.75 (0.40–19.02)

AR = allergic rhinitis; CI = confidence interval; CRS = chronic rhinosinusitis; OR = odds ratio; SD = standard deviation.

TABLE 3. Obstructive sinonasal anatomic variants

	AR patients, mean (SD)	AR-CRS patients, mean (SD)	Univariate <i>p</i> value	Univariate OR (95% CI)	Multivariate <i>p</i> value	Multivariate OR (95% CI)
Infraorbital (Haller) cells (%)	19.2 (7.7)	65.2 (9.9)	0.002	7.87 (2.14–28.87)	0.013	6.27 (1.46–26.87)
Concha bullosa (%)	19.2 (7.7)	41.7 (10.1)	0.090	3.00 (0.84–10.67)	0.988	0.98 (0.09–10.38)
Frontal intersinus cell (%)	4.0 (3.9)	47.8 (10.4)	0.005	22.00 (2.53–191.00)	0.011	18.37 (1.93–175.04)
Kuhn cell class (%)			0.010	2.08 (1.19–3.64)	0.424	1.37 (0.63–2.95)
0	36.0	30.4				
1	44.0	4.3				
2	16.0	21.7				
3	4.0	43.5				
4	0.0	0.0				

AR = allergic rhinitis; CI = confidence interval; CRS = chronic rhinosinusitis; OR = odds ratio; SD = standard deviation.

the AR-CRS cohort with concha bullosa had concomitant mucosal thickening in the ipsilateral maxillary or anterior ethmoid sinuses on CT scan at the time of CRS diagnosis. We found that 19.2% of AR patients had at least 1 infraorbital cell in comparison to 65.2% of AR-CRS patients, reflecting a significant association of infraorbital cells with progression to CRS on univariate ($p = 0.002$) and multivariate ($p = 0.013$) regressions, reflecting an OR of 6.27 for development of CRS in AR patients who have an infraorbital cell. Of patients in the AR-CRS cohort who had an infraorbital cell, 81% had concomitant mucosal thickening in the ipsilateral maxillary sinus on CT scan at the time of CRS diagnosis.

In the frontal recess, the average highest Kuhn class of anterior ethmoid cells from either the right or left side was 0.88 in the AR cohort and 1.78 in the AR-CRS cohort. There was a significant association between higher Kuhn class and development of CRS on univariate regression ($p = 0.010$), but not on multivariate regression ($p = 0.424$). We found frontal intersinus cells in 4.0% of the AR cohort and 47.8% of the AR-CRS cohort, reflecting a statistically significant association with development of CRS on univariate

($p = 0.005$) and multivariate ($p = 0.011$) regressions. Although presence of a frontal intersinus cell corresponded to an OR = 18.37 for development of CRS, only 50% of patients in the AR-CRS cohort with a frontal intersinus cell demonstrated mucosal thickening in the frontal sinuses on CT scan at the time of CRS diagnosis.

We therefore considered whether infraorbital cells and frontal intersinus cells were correlated, leading to an artifactual association of CRS to frontal intersinus cells. The presence of infraorbital cells seemed to correlate with the presence of frontal intersinus cells (OR = 3.9, $p = 0.088$, Fisher's exact test). Thus it is possible that some correlation with the presence of infraorbital cells may explain the apparent significance for frontal intersinus cells in predicting progression to CRS.

Discussion

Treatment for CRS is centered around symptom control rather than complete cure. Prevention has not been a focus of management because factors to predict those at risk prior to diagnosis of CRS are not well established. CRS

is hypothesized to arise from any number of instigating, inflammatory processes that progress to the same clinical endpoint. Previous work has established an association between AR and CRS.^{4,6,7} While the link between AR and CRS may not be causal, we hypothesize that AR may produce an inflammatory milieu in the sinonasal mucosa that, in the presence of certain risk factors, may lead to development of CRS.

In this study, we identify objective risk factors that may be used in clinical practice to identify patients with AR who are at risk for development of CRS. Although our study is retrospective in nature, the vast majority of clinicodemographic factors we sought were readily available as a common part of the allergy workup. We considered medical comorbidities often associated with CRS^{6,11,12,15} and found no strong associations with progression of AR to CRS. This may be due to the fact that conditions such as asthma or aspirin sensitivity, while associated with CRS, are related to an underlying atopic state that is also common in those with AR. Alternatively, the presence of some comorbid conditions such as nasal polyposis or aspirin sensitivity may reflect distinct inflammatory conditions that contribute to the development of CRS in the setting of AR, which our study may be underpowered to detect.

In contrast, our assessment of sinonasal anatomic variants revealed significant associations between progression to CRS and the presence of either infraorbital cells or frontal intersinus cells, which are associated with obstruction of outflow from the maxillary and frontal sinuses, respectively.^{16,17} In the past, the presence of these anatomic variants has not been found to be associated with patients who have CRS.^{16,20,21} However, these studies have not focused on specific subsets of patients with CRS. In contrast, we have examined a specific subset of CRS patients, namely those with AR that preceded CRS. In this particular subset of patients, the presence of obstructive anatomic variants in the setting of allergic sinonasal inflammation may be contributory to the development of CRS. It is similarly possible that the study of other specific CRS patient subsets may reveal a significant association between the presence of these anatomic variants and the development of CRS.

Moreover, in addition to infraorbital cells and frontal intersinus cells, we additionally observed trends toward insignificant association for other potentially sinonasal obstructive variants. The presence of these anatomic variants largely correlated to mucosal thickening in the corresponding sinuses on CT scans obtained at the time of CRS diagnosis. In the case of frontal intersinus cells, which correlated with frontal sinus mucosal thickening only 50% of the time, we hypothesize that because CT scans capture a picture of CRS at only 1 time point, any role in development of CRS may have occurred prior to imaging. Alternatively, we find that an unknown correlation between the presence of infraorbital cells and frontal intersinus cells may have lead to a noncausal, statistically significant association of CRS development and the frontal intersinus cells.

Patients with AR are frequently treated solely by a primary care physician, and it is important to consider why these patients may have sought a multidisciplinary evaluation by an allergist and otolaryngologist, because it is possible that these patients had particularly severe or constant sinonasal symptoms. This is supported by the fact that many of these patients had previous sinus CT scans, which are not routinely performed in the workup of simple AR. Moreover, because not all patients in our AR cohort had a CT scanned performed, it is likely that those patients in the AR cohort who did have CT scans performed were patients with more severe sinonasal symptoms and the diagnosis of CRS was being ruled out with imaging studies at the time of presentation. A potential skew in our study population toward patients with more severe sinonasal symptoms may artificially inflate the prevalence of comorbid conditions or characteristics (either medical or anatomical), which may be illustrated by the high prevalence of both seasonal and perennial AR. Overall, this effect would make identification of CRS risk factors more difficult. Detection of CRS risk factors is also made difficult because patients in our AR cohort, which we consider to represent AR patients who do not progress to CRS, may nonetheless progress to CRS at a later point in time. Although we would expect the effect of such confounding issues to be minimized with larger cohort sizes, given these challenges, the risk factors that we have been able to identify appear all the more significant. With larger cohorts of patients with AR and even longer follow-up times it would not be surprising to find other anatomic or clinical risk factors for development of CRS.

This is the first study to evaluate and identify objective risk factors for development of CRS in patients with AR and our findings have important implications. We have identified putatively obstructive sinonasal anatomical variants as potential CRS risk factors that are easily assessed in clinical practice on CT scan, which may be obtained for AR patients who have particularly severe sinonasal symptoms or poor response to medical therapy and radiologic studies are obtained to investigate for the possibility of chronic rhinosinusitis. Our findings provide motivation for and warrant performance of further prospective study. For now, however, we suggest that identification of any of these potential CRS risk factors in a patient with AR may, in the context of the clinical presentation: (1) inform the decision to pursue more aggressive medical treatment of AR as a rational attempt to prevent progression to CRS; and (2) serve as a discussion point with patients in the course of counseling stringent compliance with their therapy.

Conclusion

AR, in the right setting, may lead to the development of CRS. We have identified 2 potentially obstructive sinonasal anatomic variants as characteristics associated with patients who initially presented with AR and subsequently developed CRS. Easily assessed with imaging, these variants

may identify AR patients at increased risk for development of CRS and thus may need more aggressive management of their AR. The ability to inform patients of this risk might

increase their adherence to treatment regimens or influence the decision to pursue other treatment options, such as allergen immunotherapy. ④

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