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Aeroallergen sensitivities and development of chronic rhinosinusitis in thirteen adults who initially had allergic rhinitis

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Dear Editor,

Based on common comorbidity, immunologic mediators and symptomatology, there exist reported epidemiologic and pathophysiologic links between allergic rhinitis (AR) and chronic rhinosinusitis (CRS).¹⁻³ In addition, AR has previously been associated with individuals who develop CRS.⁴ While it has previously been reported that obstructive sinonasal variants may be associated with the development of CRS in adults with AR^{5,6}, the relationship between the degree of atopy and development of CRS in adults remains uncharacterized.

We hypothesized that the aeroallergen sensitivity profile of AR patients—in particular the number of aeroallergen sensitivities—may impact the subsequent development of CRS. We explore this hypothesis here by evaluating the aeroallergen sensitivity profile of adult patients who have been managed long-term for AR without development of CRS and compare it to that of a cohort of thirteen adult AR patients who subsequently developed CRS. This latter cohort of AR patients, whose development CRS was clinically tracked, has been culled from many years of long term management of AR patients and provides a unique opportunity to learn about factors associated with the development of CRS in patients with AR.

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, aged 18 and older, presenting between March 2004 and November 2011 and diagnosed with AR (with associated ICD-9 codes 477.*) but not CRS (ICD-9 codes 473.*) was retrospectively screened for inclusion into one of two cohorts. All patients followed for at least four or more years without meeting guideline-established criteria^{2,7} for the diagnosis of CRS comprise the AR cohort, which represents AR patients who do not

develop CRS. A second cohort, referred to as the AR-CRS cohort, is comprised of AR patients who developed CRS (based on guideline-established criteria^{2,7}) after a minimum of six months of follow-up. In all cases, the diagnosis of allergic rhinitis was dependent on symptomatology and positive skin prick or serological testing. Inclusion criteria included availability of allergy testing results to grasses, trees, weeds, molds, dust mites, cockroach, cat, and dog. Clinical and demographic data were recorded in a blinded manner and consisted of information that is commonly collected as a part of a routine AR workup, including age, gender, aeroallergen sensitivity profile and comorbid asthma.

Statistical analysis

All analysis was performed with the statistical software package R (www.r-project.org). Associations between development of CRS and predictor variables were determined with the logistic regression and Cox proportional hazard analysis in the rms package. Multivariate logistical analysis was performed using all predictor variables with $p \leq 0.100$ in the univariate regression **in addition to age and gender**. In the multivariate model, significant predictors were identified via backwards elimination, using a p value cut-off of 0.100. Cross validation was performed through bootstrapping of the dataset using the `validate()` function from the rms package over 100 iterations. For each variable retained in the final model, a p value and either a log-odds ratio or hazard ratio were calculated. P values less than 0.05 were considered significant.

Results

Patient characteristics

The clinical and demographic characteristics of patients meeting inclusion criteria were collected and recorded (Table 1). A total of 23 patients were identified for the AR cohort and 13 patients were identified for the AR-CRS cohort. **In the AR cohort, 16 patients (69.6%) had a CT scan and 9 patients (69.2%) in the AR-CRS cohort had a CT scan while carrying only a diagnosis of AR**

(prior to being diagnosed with CRS). All of these CT scans, performed on patients carrying the diagnosis of AR, were inconsistent with CRS. Patients in the AR cohort were followed for a median of 6.2 years (range 4.2 – 12.2 years) without development of CRS. Patients in the AR-CRS cohort were followed for AR and developed CRS at a median of 3.5 years (range 0.5 – 8.4 years) after the initial presentation for AR. None of the patients in either cohort was a smoker. At the time of development of CRS diagnosis, only one out of the thirteen patients had evidence of nasal polyps.

There were no statistically significant differences in clinical or demographic characteristics between the two cohorts. In both cohorts, dust mite sensitivity was the most common (87.0% in the AR cohort and 61.5% in the AR-CRS cohort) indoor sensitivity and trees were the most common outdoor sensitivity (73.9% in the AR cohort and 61.5% in the AR-CRS cohort).

Association between aeroallergen sensitivity and development of CRS

Aeroallergen sensitivities were tested for association with development of CRS in patients with AR (Table 2). Only a statistically significant association was found for cat sensitivity, which was found to be negatively associated with development of CRS (odds ratio = **0.22**, 95%CI: **0.05 – 0.99**, **p = 0.048**) as well as the temporal progression to CRS (hazard ratio = **0.29**, 95%CI: **0.09 – 0.96**, **p = 0.043**). The total number of aeroallergen sensitivities, although greater in the AR cohort, was not associated with development of CRS (odds ratio = 0.75, 95%CI: 0.49 – 1.13, **p = 0.167**) or the temporal progression to CRS (hazard ratio = 0.81, 95%CI: 0.58 – 1.12, **p = 0.207**).

Discussion

Synopsis of key findings and comparison with other studies

It has been suggested that AR may be a predisposing factor for development of CRS^{3,4}. If this is the case it is possible that the degree of atopy, as measured by the number of aeroallergen sensitivities, may be associated with the development of CRS in patients with AR. Although this has not been shown to be the case in children with AR,⁸ it remains unclear whether this is the case in

adults with AR. In the present study we did not find the number of aeroallergen sensitivities to associate with development of CRS in adult AR patients.

The aeroallergen sensitivity profiles of our patient cohorts were nonetheless consistent with previous studies of AR and CRS patients, with dust mites and trees amongst the most prevalent perennial and seasonal aeroallergen sensitivities, respectively.^{9,10} Additionally, although we did not find a statistically significant relationship between the number of aeroallergen sensitivities and the development of CRS in AR patients, the point-estimates from our results do not even suggest a potentially meaningful, positive association. The general trends in our data suggest that adults with AR who do not go on to develop CRS tend to have more aeroallergen sensitivities than adults who do develop CRS, which is what has been previously found in children with AR as well.⁸ We have additionally found that cat sensitivity is negatively associated with development of CRS in this patient cohort. It remains unclear whether this is related to some unknown, protective mechanism of cat sensitivity or whether this is simply a reflection of the general trend towards negative associations between sensitization and development of CRS in patients with AR.

Strengths of this study

This study is the first to directly investigate the association of the aeroallergen sensitivity profile of adult AR patients and the subsequent development of CRS. Although previous studies have examined the atopic characteristics patients with AR and CRS, these studies cannot be interpreted with respect to the development of CRS. In contrast, our study includes a unique cohort of AR patients who have been clinically followed to the development of CRS. This cohort therefore provides a special opportunity to study the development of CRS in patients with AR.

Limitations of this study

Our study is limited by its retrospective nature as well as the small numbers of patients included, due to the stringency of our follow-up time inclusion criteria and difficulty in following enough AR patients long enough to detect the small percentage that will eventually develop CRS.

Most but not all patients in the AR and AR-CRS cohorts underwent a CT scan while diagnosed with only AR. Because the symptomatology of AR and CRS may overlap it is possible that in some patients, who did not undergo a sinus CT scan while diagnosed with only AR, objective evidence of sinusitis was missed. Additionally, although we are unable to directly account for AR medication use, all patients were nonetheless prescribed medications for AR based on their clinical presentations. Despite these limitations, this study nonetheless provides preliminary results about the relationship between aeroallergen sensitization and development of CRS in patients with AR, which will inform the design and powering of future prospective study on this important question.

Conclusion

No association between development of CRS in patients with AR and the degree of atopy, as measured by the number of aeroallergen sensitivities, has been found in this study. On the contrary, trends within our results suggest that a greater degree of atopy exists in AR patients who do not develop CRS in comparison to those who do. Although the degree of atopy may nonetheless contribute to the development of CRS in patients with AR, our results suggest that other contributory factors should be sought as well. Further study on the association of aeroallergen sensitivities and development of CRS in AR patients is warranted.

Key points

- Allergic rhinitis and chronic rhinosinusitis lead to similar sinonasal symptomatology, and common immunologic processes may mediate both conditions.
- Aeroallergen sensitivity and allergic rhinitis may precede the diagnosis of chronic rhinosinusitis in some patients and previous studies have identified allergic rhinitis as a risk factor for development of chronic rhinosinusitis.
- Between patients with allergic rhinitis who do not develop chronic rhinosinusitis and those who do, our results do not find a difference in the number of aeroallergen sensitivities.
- In our small cohort, we find that cat sensitivity is associated with a lower probability of developing chronic rhinosinusitis in patients with allergic rhinitis.
- Although larger scale studies are needed to further characterize the relationship between aeroallergen sensitivities in allergic rhinitis patients and the subsequent development of chronic rhinosinusitis, our preliminary results suggest that factors beyond just the degree of atopy, as measured by aeroallergen sensitivities, should be considered when monitoring allergic rhinitis patients for development of chronic rhinosinusitis.

References

1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the world health organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63 Suppl 86:8-160.
2. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl*. 2012;(23)(23):3 p preceding table of contents, 1-298.

3. Georgalas C, Vlastos I, Picavet V, van Drunen C, Garas G, Prokopakis E. Is chronic rhinosinusitis related to allergic rhinitis in adults and children? applying epidemiological guidelines for causation. *Allergy*. 2014;69(7):828-833.
4. Tan BK, Chandra RK, Pollak J, et al. Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis. *J Allergy Clin Immunol*. 2013;131(5):1350-1360.
5. Sedaghat AR, Gray ST, Wilke CO, Caradonna DS. Risk factors for development of chronic rhinosinusitis in patients with allergic rhinitis. *Int Forum Allergy Rhinol*. 2012;2(5):370-375.
6. Sedaghat AR, Gray ST, Chambers KJ, Wilke CO, Caradonna DS. Sinonasal anatomic variants and asthma are associated with faster development of chronic rhinosinusitis in patients with allergic rhinitis. *Int Forum Allergy Rhinol*. 2013;3(9):755-761.
7. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: Adult sinusitis. *Otolaryngol Head Neck Surg*. 2007;137(3 Suppl):S1-31.
8. Sedaghat AR, Phipatanakul W, Cunningham MJ. Atopy and the development of chronic rhinosinusitis in children with allergic rhinitis. *J Allergy Clin Immunol Pract*. 2013;1(6):689-691.
9. Gutman M, Torres A, Keen KJ, Houser SM. Prevalence of allergy in patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2004;130(5):545-552.
10. Van Lancker JA, Yarnold PA, Ditto AM, et al. Aeroallergen hypersensitivity: Comparing patients with nasal polyps to those with allergic rhinitis. *Allergy Asthma Proc*. 2005;26(2):109-112.

Conflict of interest

A.R.S. is a consultant for Meda Pharmaceuticals, which is not affiliated with this study and did not provide financial support for this work.

Table 1. Patient characteristics

	AR Patients (n = 23)	AR-CRS Patients (n = 13)	p value
Demographics			
Age¹ , mean (years)	43.7 years	44.5 years	0.844
Gender (%)			1.00
Male	43.5%	46.2%	
Female	56.5%	53.8%	
Clinical characteristics			
Asthma (%)	39.1%	53.8%	0.493
Aeroallergen sensitivities			
Grass	47.8%	46.1%	
Tree	73.9%	61.5%	
Weeds	43.5%	53.8%	
Molds	34.8%	30.8%	
Dust mites	87.0%	61.5%	
Cat	69.6%	30.8%	
Dog	39.1%	23.1%	
Cockroach	13.0%	15.4%	
Number of sensitivities, (mean)	4.1	3.2	0.180
0 – 4 sensitivities	65.2%	69.2%	
>4 sensitivities	34.8%	30.8%	

¹At the initial presentation

Table 2. Relationship between aeroallergen sensitivities and development of CRS

	Association				Time to development of CRS			
	Univariate		Multivariate ¹		Univariate		Multivariate ¹	
Aeroallergen sensitivity	OR ²	p value	OR	p value	HR ³	p value	HR	p value
Grass	0.93 (0.24 – 3.65)	0.923			0.83 (0.28 – 2.47)	0.732		
Tree	0.56 (0.13 – 2.42)	0.441			0.64 (0.21 – 1.96)	0.435		
Weeds	1.52 (0.39 – 5.95)	0.550			1.38 (0.72 – 4.20)	0.568		
Molds	0.83 (0.19 – 3.58)	0.806			0.86 (0.26 – 2.79)	0.799		
Dust mites	0.24 (0.05 – 1.15)	0.090	—	0.562	0.44 (0.14 – 1.34)	0.147		
Cat	0.19 (0.04 – 0.85)	0.030	0.22 (0.05 – 0.99)	0.048	0.29 (0.09 – 0.94)	0.039	0.29 (0.09 – 0.96)	0.043
Dog	0.47 (0.24 – 0.89)	0.332			0.60 (0.16 – 2.19)	0.440		
Cockroach	1.21 (0.18 – 8.39)	0.846			1.99 (0.50 – 9.43)	0.384		
Number of sensitivities	0.75 (0.49 – 1.13)	0.167			0.81 (0.58 – 1.12)	0.207		

¹Controlling for age and gender

²OR = odds ratio

³HR = Hazard ratio