

The association of allergic sensitization with radiographic sinus opacification

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ABSTRACT

Background: The relationship between allergic sensitization and radiographic sinus inflammation remains unclear.

Objectives: To determine whether specific allergen sensitization is correlated with sinonasal radiographic opacification.

Methods: Patients with chronic sinonasal symptoms were selected and included if they had allergy testing and a computed tomography (CT) of the paranasal sinuses. Data regarding demographic characteristics, *in vitro* allergy test results, and comorbidities were collected. CTs were reviewed, and an overall Lund-Mackay score (LMS) was calculated for each patient. A two-sample *t*-test was used to compare mean LMS between patients who were sensitized and patients who were not sensitized. A multiple linear regression model was used to determine whether a relationship existed among LMS and allergy results, asthma, nasal polyps, immunoglobulin E (IgE) level, medication usage, in-season versus out-of-season CTs, age, and sex. Significance was determined at an alpha level of 0.05.

Results: There were 437 patients included, of whom, 251 had positive specific allergen test results and 186 had negative test results. A total of 282 patients had allergic rhinitis symptoms without a documented diagnosis of sinusitis, and 155 carried a diagnosis of chronic rhinosinusitis. The mean LMS did not differ between patients who were sensitized and patients who were not sensitized (5.56 versus 5.28; $p = 0.61$). Linear regression demonstrated an increase in LMS in patients with asthma ($p = 0.02$), male sex ($p < 0.01$), elevated IgE ($p < 0.01$), a history of anaphylaxis ($p = 0.03$), and nasal polyps ($p < 0.01$). There was a statistically significant decrease in LMS in patients with an in-season CT ($p = 0.02$).

Conclusions: Patients with a positive specific *in vitro* allergen test result did not have higher overall rates of radiographic sinus inflammation. Asthma, male sex, polyps, elevated IgE, and a history of anaphylaxis were associated with higher LMS.

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The relationship between chronic rhinosinusitis (CRS) and allergic rhinitis (AR) is poorly characterized. Both AR and CRS are common chronic airway diseases. AR affects between 10 and 30% of adults in the United States and an even higher proportion of children in industrialized nations.¹ CRS is less prevalent than AR, with an estimated 10–15% of adults affected in the United States.^{2,3} Allergic sensitization, or having specific immunoglobulin E (IgE) mediated response to allergens, is seen in all patients with AR, but it has also been found in high percentages in patients with CRS in studies, with an unknown significance.^{4,5} Because both diseases are common and there is often overlap between AR and CRS symptoms, many investigators have sought to determine a relationship between CRS and AR, with varying indirect assessments and conflicting results as to whether AR contributes to CRS pathogenesis.^{6–20} Results of some studies demonstrate a significant contributory relationship,^{7–15} whereas other studies demonstrate no causal relationship between AR and CRS.^{17–21} The role of allergic inflammation in the pathogenesis of CRS remains unclear, but there has been speculation that inflammation and swelling from allergic disease may spill over and contribute to the development of CRS by leading to inflammation and obstruction at the sinus ostia, with subsequent mucous retention and infection.¹⁸

This study aimed to establish a correlation between allergic sensitization and sinus opacification in patients with CRS and AR by

comparing sinus computed tomography (CT) Lund-Mackay scores (LMS) in patients who were sensitized and patients who were not sensitized, and then correlating opacification with the class of allergen sensitization. A correlation between the LMS and overall sinus symptoms has been proven to be insignificant,^{22–24} but the LMS is predictive of markers of sinonasal inflammation, such as improvement in the 22-item Sino-Nasal Outcome Test scores after surgery, the extent of surgery, rate of complications, sinus drainage, nasal edema, and polyp burden.^{22,23} Although it is not a predictor of quality of life or sinusitis severity, the LMS does allow for an objective measurement of sinus swelling and comparison with the general population, which has an average LMS of 4.3.²⁵

METHODS

Institutional review board approval was obtained at Boston University Medical Center (study H-32860). Patients were retrospectively identified for inclusion in the study if they had presented with sinonasal symptoms and underwent both *in vitro* hypersensitivity testing and a paranasal sinus CT between 2006 and 2010. Indications for allergy testing were sinonasal symptoms, including rhinorrhea, congestion, sneezing, postnasal drip, sinusitis, and a clinical suspicion of atopic disease as determined by the treating provider. Indications for ordering a CT were generally for evaluation of paranasal sinus disease, and the determination to order a CT was made by the treating physician. Demographic data as well as the comorbidities of asthma (self reported by patients during a history taking and physical examination), anaphylaxis history, nasal polyps (diagnosed by the physician by endoscopy), and medication usage at the time of allergy testing (including nasal steroids, oral antihistamines, and oral steroids) were collected on the patients. No patients included in the study were on oral steroids within 3 months of allergy testing.

The patients were divided into two groups of patients with rhinitis and patients with sinusitis. Those with rhinitis, identified by The International Classification of Diseases, Ninth Revision code as chronic rhinitis (472.0) or AR (477.xx), and those with sinusitis were identified by the code for chronic rhinosinusitis (473.xx). If the patients carried both diagnoses, then they were placed in the CRS

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group. Patients were excluded if they had undergone sinus surgery before the CT examination, were on immunotherapy at any point during the data collection period, or if they had a systemic condition associated with chronic sinusitis (Wegener disease, cystic fibrosis, or sarcoidosis). *In vitro* testing results were used due to an institutional physician practice pattern of preferentially obtaining *in vitro* testing instead of skin testing. Blood was drawn on site and sent out to a commercial laboratory for analysis. Allergy testing was performed by *in vitro* testing with enzyme-linked immunosorbent assay (ImmunoCAP, Phadia, Sweden) for 27 inhalant allergens, and a value of 0.35 kUA/L was used as the cutoff for a positive test result.

CTs were examined and LMS were calculated for every patient by evaluators (C.B., M.P.) blinded to the results of patient's allergy testing. If multiple CTs were identified, then the CT performed closest to the time of allergy testing was used. LMS was calculated by using a 0–2 grading scale for the maxillary, ethmoid, sphenoid, and frontal sinuses bilaterally: 0 was given for no opacification, 1 for partial opacification, and 2 for complete opacification. For the osteomeatal complex, a score of 0 or 2 was given for patent or obstructed. For patients with hypersensitivity to seasonal allergens, the patients were also identified as having had their CT during the season of their allergic sensitization or outside of their sensitivity season. For practical purposes, allergy seasons were categorized by a 3-month period around the time when there is peak pollen present (*i.e.*, for trees, March, April, May). The mean LMS was calculated and compared between patients in season and out of season by using a two-sample *t*-test. Perennial allergens were defined as mold, epidermal, insect (cockroach), and house dust mite allergens.

Statistical analysis was performed by using Statistical Analysis Software version 9.3 (SAS Institute, Inc., Cary, NC). The mean LMS was compared between patients with atopy and those patients without atopy as well as between those with rhinitis and those with sinusitis diagnoses by using a two-sample *t*-test. To examine the associations among the dependent variable, LMS, and the predictor variables: rhinitis diagnosis; IgE level; anaphylaxis history; age; asthma; polyps; male sex; positive sensitization to weeds, grass, trees, dust, insect, or epidermal allergens; in-season CT; use of nasal steroids; and use of oral antihistamines (no patients were on oral steroids within 3 months of allergen testing, and this was left out of the analysis), a multiple linear regression analysis was performed. Variables in the linear regression model were selected based on clinical relevance. Significance was determined at $\alpha = 0.05$.

RESULTS

There were 437 patients included, of whom, 251 had positive specific allergen test results and 186 had negative test results; 282 had rhinitis symptoms without sinusitis and 155 carried a diagnosis of CRS (Table 1). Of the 251 patients with positive specific allergen test results, 41 had seasonal sensitivities only, 84 had perennial sensitivities only, and 126 had both (Fig. 1). The mean LMS did not differ between patients who were sensitized and patients who were not sensitized (5.56 versus 5.28, respectively; $p = 0.59$). The mean LMS

was significantly higher in the sinusitis group compared with the patients with rhinitis (8.3 versus 4.0, respectively; $p < 0.01$). The linear regression analysis resulted in an R^2 value of 0.35, which indicated that the variables used in the regression model accounted for ~35% of the variability in the LMS. The overall model was significant, with $p < 0.01$. There was an association between an increase in LMS in patients with asthma ($\beta = 1.35$, $p = 0.02$), elevated IgE level ($\beta < 0.01$, $p = 0.04$), anaphylaxis ($\beta = 4.70$, $p = 0.03$), male sex ($\beta = 1.98$, $p < 0.01$), and polyps ($\beta = 5.03$, $p < 0.01$). Age, positive allergen class, and medication usage were not associated with a higher LMS. A diagnosis of rhinitis (as opposed to sinusitis) ($\beta = 3.49$, $p < 0.01$) and an in-season CT were associated with a lower LMS ($\beta = 2.54$, $p = 0.02$) (Table 2).

DISCUSSION

In this large series of patients with chronic rhinitis and CRS, objective data from sinus CTs and *in vitro* allergy testing did not demonstrate a relationship between allergic sensitization and sinonasal opacification on CTs. Linear regression did demonstrate an increase in LMS for patients with a history of anaphylaxis, asthma, polyps, elevated IgE, and male sex. The radiographic opacification associated with asthma and nasal polyps is expected, given the known association of these conditions with sinusitis. Although they met criteria for significance, elevated IgE levels did not have a major impact on overall LMS ($\beta < 0.01$), and a history anaphylaxis was only present in five patients in the series, which limited the generalizability of these findings. Unsurprisingly, the diagnosis of rhinitis was associated with a decreased LMS when compared with a diagnosis of sinusitis, which confirmed the impact of sinusitis on CT opacification. There was no impact on LMS from specific allergen class sensitization. For patients with seasonal sensitizations, the timing of the CT in relation to allergen season did not show any significant increase in overall LMS and actually was associated with a decrease in LMS, which indicated that sinus imaging would be unbiased by the timing of CT with regard to the patient's seasonal allergens. The use of antihistamines and nasal steroids was not associated with a difference in LMS.

Several studies have been published that demonstrate an increase in sinonasal inflammation in patients with CRS and with allergy when compared with those with CRS without allergy.^{7–13} There is published evidence to support that patients with nasal polyposis have a higher rate of perennial allergen sensitization than do patients without polyps¹² and that these patients have higher rates of sensitization overall.¹¹ Other investigators have performed endoscopy, CT, and allergy testing on patients with CRS and on normal controls, and noted significantly more inflammation on CTs in the patients with allergy than in the patients without allergy,^{7,8} and treatment of allergic sensitization with immunotherapy seems to have some benefit in treatment of CRS.¹⁴ One study found increased CT grading scores in patients with allergic sensitization, which noted more patients with hypersensitivity to perennial allergens in the group with higher graded CTs,⁵ whereas another study demonstrated increased severity of sinus disease with increased skin end point

Table 1 Demographic characteristics (total cohort, N = 437)

	Rhinitis Group (n = 282)		Sinusitis Group (n = 155)		p Value
	Atopic (n = 155 [35.5%])	Nonatopic (n = 127 [29.1%])	Atopic (n = 96 [22.0%])	Nonatopic (n = 59 [13.5%])	
Sex, no. (%)					
Women	57 (13.0)	42 (9.6)	36 (8.2)	19 (4.3)	
Men	98 (22.4)	85 (19.5)	60 (13.7)	40 (9.2)	
Age		41.3		40.3	0.58
Lund-Mackay score		4.0		8.3	≤0.01
	4.2	3.4	7.7	9.4	

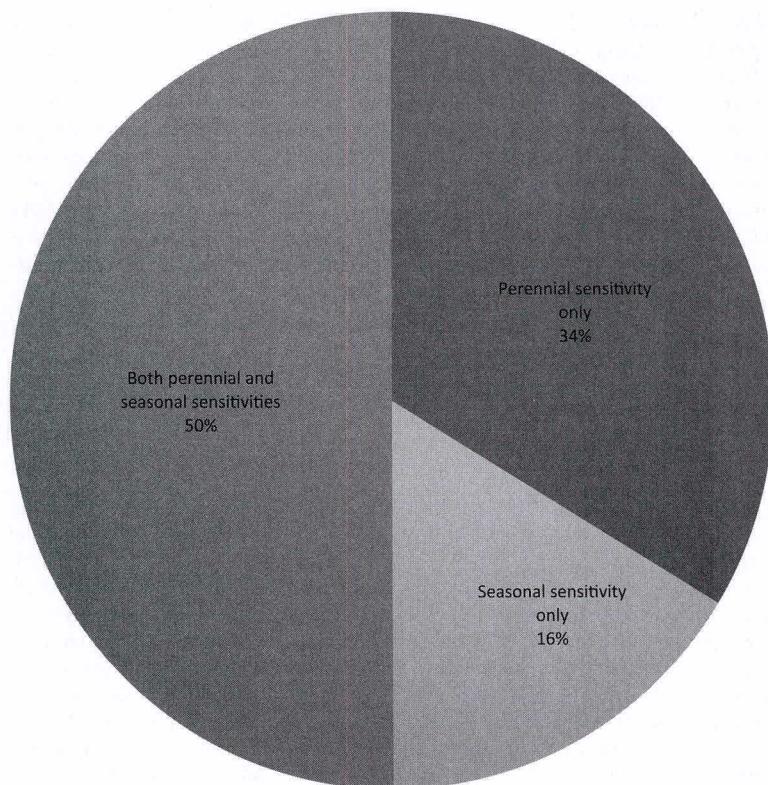


Figure 1. The total number of patients with allergen sensitization was $n = 252$: 41 patients had seasonal sensitization only, 84 had perennial sensitization only, and 126 patients had both perennial and seasonal sensitizations.

Table 2 Results of linear regression model*

Variable	β Value (effect size)	Standard Error	t Value	p Value
Intercept	5.52	0.89	6.19	<0.01*
Rhinitis	-3.49	0.49	-7.11	<0.01*
Sex	1.98	0.49	4.05	<0.01*
IgE	<0.01	<0.01	2.07	0.04*
In-season CT	-2.54	1.11	-2.30	0.02*
Antihistamines	-0.74	0.61	-1.21	0.23
Nasal steroids	0.68	0.51	1.33	0.18
Age	0.01	0.02	0.77	0.44
Polyps	5.03	0.66	7.68	<0.01*
Anaphylaxis	4.70	2.18	2.15	0.03*
Asthma	1.35	0.56	2.40	0.02*
Tree	-0.28	0.93	-0.30	0.77
Grass	0.74	0.85	0.88	0.38
Weed	1.47	0.90	1.63	0.10
Dust	-0.90	0.57	-1.57	0.12
Mold	-0.49	0.84	-0.58	0.56
Epidermal	0.74	0.67	1.10	0.27
Insect	0.42	0.68	0.62	0.53

IgE = Immunoglobulin E; CT = computed tomography.

*The overall model was significant ($p < 0.01$), and the R^2 value was 0.35.

titration allergy testing, which indicated that allergic disease contributes to the severity of CRS.⁴

However, an equally robust segment of studies in the literature found no relationship between allergy and CRS.¹⁷⁻¹⁹ Robinson *et al.*,¹⁷ noted that, in patients with CRS, the allergic status did not influence the 20-item Sino-Nasal Outcome Test scores or the revision surgery rate, but CT scores were higher in the atopic group. Another group found that atopic status did not influence the prevalence of CRS or asthma between the groups and that patients with atopy actually had

lower CT grading scores.¹⁸ Erbek *et al.*,¹⁹ similarly found no association among the presence of sensitization and polyp size, CT opacification, symptom scores, or recurrences.

Overall, the results of this study did not find a relationship between allergic sensitization and radiographic sinus opacification. In addition, an in-season CT was not associated with an increased LMS and was actually associated with a decreased LMS. This finding indicated that the impact of seasonal allergic disease on CRS may be limited to symptomatic deterioration in season without a contribution to the

severity of year-round sinus inflammation and radiographic opacification, which is in contrast to previous studies that showed increased eosinophilia in the sinuses during an allergen season,⁹ and which indicated that, although allergic inflammation may be present, it may not translate into radiographic findings. Analysis of the results also indicated that the perennial allergens, including house dust mites, cockroach, epidermal allergens, and molds, did not contribute to radiographic opacification in the paranasal sinuses.

When taken together, the findings discussed in this article supported the assumption that sinus opacification was not related to allergic sensitization. There were limitations to this study. Our goal was to measure the impact of allergic sensitization on paranasal sinus inflammation *via* LMS and sinus opacification, but, because all the patients in this study had some degree of nasal symptoms, some of the underlying opacification may have come from the differing disease processes, whether or not allergy mediated. Allergy testing was not performed on a random population, and, therefore, there may have been a bias toward testing patients with more significant sino-nasal symptoms, which would likely increase the overall LMS of both the population of patients who were not sensitized and patients who were sensitized when compared with an asymptomatic control group. Treatment of these patients before allergy testing and CT was not standardized, although the use of nasal steroids and antihistamines did not correlate with LMS in the regression model.

CONCLUSION

Allergen sensitization to seasonal and perennial allergens did not influence the overall LMS, and the timing of CT in relation to allergy season did not seem to increase the LMS. Asthma, nasal polyps, and male sex were associated with an increase in LMS.

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