

Atopy and the development of chronic rhinosinusitis in children with allergic rhinitis

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Clinical Implications

- The role of allergic rhinitis in the development of chronic rhinosinusitis in children remains unknown.
- This study demonstrates the degree of atopy, as reflected by the number of aeroallergen sensitivities or the presence of atopic comorbidities, is not associated with progression to chronic rhinosinusitis in the pediatric age group.

TO THE EDITOR:

Allergic rhinitis (AR) has previously been associated with chronic rhinosinusitis (CRS) by virtue of similar inflammatory profiles and increased prevalence of AR in patients with CRS.^{1,2} Logistical issues, such as requisite follow-up time and cohort sizes, render impractical longitudinal studies of pediatric patients to detect the impact of AR on the development of CRS. In adults, the study of associations with CRS development in patients with AR, however, has been feasible and provided some insight.^{3,4} From the common clinical presentations of AR and CRS, it is reasonable to hypothesize that, in children with AR, atopic characteristics, reflected by the number of atopic comorbidities or aeroallergen sensitivities, may be associated with CRS development.

We studied 2 cohorts of children with AR to identify specific characteristics potentially associated with CRS development. We identified these pediatric cohorts by screening the records of 19,186 children diagnosed with AR over a 10-year period through formal clinic evaluation and skin testing in our institution's division of allergy and immunology (see Methods in this article's [Online Repository](#) at www.jaci-inpractice.org). One cohort (N = 117), referred to as the AR cohort, is defined by at least 9 years of allergy or otolaryngology follow-up subsequent to the diagnosis of AR without a diagnosis of CRS. This AR cohort is assumed to reflect children with AR who do not develop CRS. The other cohort (N = 37), referred to as the AR-CRS cohort, consists of children diagnosed with CRS after a minimum of 1 year of allergy or otolaryngology follow-up subsequent to an initial diagnosis of AR and is assumed to reflect children with AR who later develop CRS. Patients in both cohorts were closely monitored, with a mean (standard deviation [SD]) of 1.4 ± 0.7 clinic visits per year for patients in the AR cohort and 3.5 ± 1.9 clinic visits per year for patients in the AR-CRS cohort over the follow-up period. Clinical, demographic, and atopic characteristics of these children were obtained and analyzed with descriptive statistics (described in this article's [Online Repository](#)) (Table I).

Although children in the AR cohort (mean [± SD], 5.4 ± 3.7 years old) initially presented at a younger age (*P* = .047) compared with children in the AR-CRS cohort (mean [± SD], 6.9 ± 3.7 years old), the children in the AR cohort (mean

TABLE I. Clinical and demographic characteristics

	AR cohort (N = 117)	AR-CRS cohort (N = 37)	<i>P</i> value
Demographics			
Age (y)*	14.9	11.0	<.001
Boys (%)	72.6	62.2	.65
Tobacco smoke exposure (%)	8.5	27.0	.03
Comorbidities (%)			
Asthma	82.9	64.9	.47
Eczema	56.4	51.4	.87
Food allergy	72.6	27.0	.008
Aeroallergen sensitivities			
Log ₁₀ [total serum IgE] (SD)†	2.6 ± 0.7	2.3 ± 0.7	.08
Molds (%)	62.4	37.8	.19
Any indoor (%)	86.3	83.8	.99
Dust mites	73.5	64.9	.77
Cats	62.4	59.5	.99
Dogs	53.8	24.3	.052
Mouse	22.2	8.1	.14
Cockroach	27.4	21.6	.68
Any outdoor (%)	67.5	48.6	.35
Trees	60.7	37.8	.19
Grasses	33.3	24.3	.56
Weeds	44.4	35.1	.60
No. (SD) sensitivities	4.8 ± 2.4	3.1 ± 2.2	<.001

*Age at the final follow-up visit.

†Total serum IgE levels were in units of U/mL; comparisons were made on log₁₀ transformed total serum IgE levels for both cohorts.

[± SD] 14.9 ± 3.8 years old) were generally older (*P* < .001) than children in the AR-CRS cohort (mean [± SD] 11.0 ± 3.6 years old) at the time of the last office visit. This is attributable to the follow-up duration criteria used to identify the 2 cohorts. Otherwise there were no statistically significant differences in the prevalence of asthma, eczema, or serum total IgE levels (Table I). Children in the AR cohort had a greater prevalence of food allergies (*P* = .008). While no specific aeroallergen sensitivity is more prevalent in either cohort (although a trend existed towards greater dog allergy in the AR cohort), children in the AR cohort had more aeroallergen sensitivities overall (*P* < .001) (Table I). A history of smoke exposure from in-home parental tobacco use was more prevalent in the AR-CRS cohort (*P* = .029) (Table I).

We assessed the children's demographic characteristics, atopic comorbidities, and aeroallergen sensitivities for association with the development of CRS by both univariate and multivariate logistic regression analyses (described in this article's [Online Repository](#)) (Table II). On univariate analysis, exposure to tobacco smoke was positively associated with progression to CRS (odds ratio [OR] 3.96 [95% CI, 1.50-10.48]). This was consistent with previous work that showed tobacco smoke both induces biofilm formation⁵ and adversely impacts nasociliary clearance.⁶ In contrast, increasing age, the presence of concurrent asthma, food allergy, and aeroallergen sensitivities were negatively associated with CRS development (Table II).

TABLE II. Association of atopic characteristics with progression to CRS*†

	Univariate OR (95% CI)	Univariate <i>P</i> value	Multivariate OR (95% CI)‡	Multivariate <i>P</i> value
Demographics				
Age§	0.69 (0.59-0.81)	<.001	0.71 (0.57-0.89)	.002
Tobacco smoke exposure	3.96 (1.50-10.48)	.006	—	
Comorbidities				
Asthma	0.38 (0.17-0.87)	.022	—	
Food allergy	0.12 (0.05-0.26)	<.001	0.06 (0.01-0.29)	.001
Aeroallergen sensitivities				
No. sensitivities	0.74 (0.62-0.88)	.001	—	
Dust mites	0.36 (0.16-0.86)	.020	—	
Dogs	0.20 (0.08-0.47)	<.001	—	
Mouse	0.25 (0.07-0.89)	.03	—	
Any outdoor	0.46 (0.21-0.97)	.041	—	
Trees	0.27 (0.12-0.60)	.001	—	

*ORs with 95% CIs are shown only for variables that met statistical significance on univariate association; variables that did not meet statistical significance on univariate analysis (and therefore not shown) are: sex; history of eczema; total serum IgE; the presence of any indoor allergy; and allergies to molds, cat, cockroach, grasses, and weeds. †Aeroallergen sensitivities were unavailable for 12 children in the AR cohort who had allergy testing performed at another institution; these 12 children were excluded from analyses that involved aeroallergen data. Thus, univariate analysis of aeroallergen sensitivities as well as multivariate analysis included 105 of the 117 patients from the AR cohort but all 37 patients in the AR-CRS cohort.

‡Odds ratios for predictor variables included in the multivariate analysis that are not statistically different from 1.0 are represented as “—.”

§Age at the final follow-up visit.

Multivariate analysis revealed only age (OR 0.71 [95% CI, 0.57-0.89]) and food allergy (OR 0.06 [95% CI, 0.01-0.29]) to be negatively associated with CRS development in children with AR (Table II). The detected negative association between increasing age and CRS development may simply reflect an artifact of the inclusion criteria used to identify each cohort. Alternatively, this negative association may suggest that pediatric CRS is more likely to occur earlier in childhood. To date, no data support this latter conclusion, whereas the former explanation is supported by the finding that food allergy was the only statistically significant characteristic associated with CRS development by multivariate Cox proportional hazard regression (hazard regression 0.26 [95% CI, 0.10-0.66]; *P* = .004) (described in this article's [Online Repository](#)).

In adults, Th1 and Th2 patterns of inflammation have been associated with CRS without polyps and with polyps, respectively.^{1,7} Such immunologic profiling in pediatric CRS has not been performed as extensively, although 1 recent study of sinonasal mucosa from pediatric patients with CRS has not revealed any particular immunologic differentiation pattern.⁸ By comparison, the immunologic profiles of food allergy may vary from classic IgE-mediated to cell-mediated delayed hypersensitivity.⁹ The negative association between food allergy and the development of CRS may reflect some as yet uncharacterized, fundamental difference in the immunologic mechanisms that underlie pediatric CRS and food allergy. This poses an interesting topic for future directed research.

In children with AR, the surprising absence of a positive association between the number of aeroallergen sensitivities or the presence of atopic comorbidities with the subsequent development of CRS suggests that the severity of atopy alone may not be positively predictive of CRS development. The detected negative association between the presence of food allergy in children with AR and subsequent development of CRS is suggestive but not necessarily indicative that children with AR who develop CRS are less atopic. However, the lack of a positive association between atopic measures and development of CRS may suggest a greater

role for infectious rather than inflammatory etiologies in the pathogenesis of pediatric CRS. Just as the pathophysiology of pediatric CRS remains largely uncharacterized, clearly so does its relationship with AR. The results of this study also may assure the parents and clinicians of children who are atopic that, although routine follow-up surveillance should be practiced, atopy alone may not fully predict an increased risk for CRS development. Other factors should be considered from a monitoring standpoint for this debilitating disease.

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METHODS

Inclusion criteria for study participants

To perform a study of clinicodemographic characteristics that might be associated with the development of chronic rhinosinusitis (CRS) in children with allergic rhinitis (AR), a population of children who reflected children with AR and who do not develop CRS (the AR cohort) were compared with a population of children that would reflect children with AR who do develop CRS (the AR-CRS cohort). The diagnosis of AR in the otolaryngology or allergy/immunology clinics at our institution is made primarily on a history, with support from skin prick testing. The diagnosis of CRS is made based on previously defined criteria of 90 days or more of upper airway and sinonasal symptoms, eg, nasal obstruction, purulent rhinorrhea, cough.

Billing records of all children evaluated at our institution were screened by using the International Classification of Diseases, Ninth Revision codes for AR (477.*) to identify 19,186 children who had been diagnosed with AR over a 10-year period between August 2002 and August 2012. From this overall population of children with AR, the AR cohort (which reflects children with AR who will not develop CRS) was defined as those children with at least 9 years of follow-up for AR (with a continued diagnosis of AR) without a diagnosis of CRS. From this same population, the AR-CRS cohort (which reflects children who initially present with AR and only later will develop CRS) was defined as those children with a minimum of 1 year of follow-up for AR (with continued diagnosis of AR) before the diagnosis of CRS. The medical charts of all patients who met these criteria were thoroughly reviewed for confirmation of inclusion into their assigned cohort. These stringent criteria were set to maximize the likelihood that the study participants included in each cohort would truly be representative of the intended populations.

Determination of patient characteristics

Patient demographic characteristics obtained from the medical record included age and sex as well as the presence of cigarette, cigar, and/or pipe smoke exposure at home (eg, via parental use), which is a routinely asked and commented on question in the allergy evaluation. Patient clinical characteristics obtained from the medical records of the allergy clinics included a history of eczema, asthma, and food allergy. Although, in many cases, confirmatory testing, such as spirometry or skin testing, for food allergens was performed, a patient was considered to have a positive history of eczema, asthma, or food allergy based on a diagnosis documented in the patient's medical record from a formal clinic evaluation at our institution's division of allergy and immunology. All patient characteristics obtained were before development of CRS.

Aeroallergen sensitivities were obtained from formal allergy testing by skin prick and intradermal testing to commercially available extracts (Greer Laboratories, Lenoir, NC; Hollister-Stier, Spokane, Wash) by using standard methods.^{E1} Aeroallergen sensitivities were broadly categorized as mites, molds, grass, trees, weeds, cockroach, mouse, cat, and dog. Mite allergy was based on positive testing to *Dermatophagoides pteronyssinus* allergen 1 (*Der p* 1), *Dermatophagoides farinae* allergen 1 (*Der f* 1), or a house dust mix. Mold allergy was based on positive testing to *Epicoccum*, *Alternaria*, *Hormodendrum*, *Aspergillus*, *Penicillium*, or *Helminthosporium*. Grass allergy was tested by using a grass mix (Kentucky blue, orchard, red top, timothy, and sweet vernal grass). Tree allergy was based on allergy to pollens

from extracts of birch, oak, elm, maple, red cedar, ash, hickory, mulberry, cottonwood, or some mixture of these extracts. Weed allergy was based on allergy to sage brush, lamb's quarter, marsh elder, yellow dock, plantain, or ragweed. Cockroach, mouse, cat, and dog allergies were based on positive testing to standard antigens. Allergy testing was performed by using extracts from all 9 allergen categories. Positive histamine and negative saline solution controls were used in all cases. Wheal diameters were measured 15 minutes after the skin test was placed in standard fashion.^{E1} A skin prick test wheal diameter at least 3 mm larger than the negative control was considered positive. Medications that might interfere with test results were withheld before skin testing (short-acting antihistamines for 3 days, long-acting antihistamines for 10 days, and cetirizine for 14 days). Patients were excluded if they had a negative histamine control.

Statistical analysis

All analysis and descriptive statistics were performed with the statistical software R (www.r-project.org). Statistical significance between the prevalence of binary characteristics between different cohorts of patients was performed by using the Fisher exact test, differences among categorical data were performed by using the χ^2 test, and differences among continuous variables were performed by using the Student *t* test. Associations between children who developed CRS and predictor variables were determined by logistic regression by using the *lrm()* function from the Regression Modeling Strategies (*rms*) package.^{E2} Predictor variables included children's demographic, clinical, and aeroallergen sensitivity characteristics.

Demographic characteristics used in association testing included age at the final clinic visit (to account for the possibility of an increased likelihood for development of any atopic disease with increasing follow-up time), sex, and a history of tobacco smoke exposure at home. Clinical characteristics included a history of asthma, eczema, and food allergy. Aeroallergen sensitivity characteristics included as predictor variables were sensitivity to molds, indoor allergens (dust mites, cat, dog, mouse, or cockroach) and outdoor allergens (trees, grass, or weeds). Aeroallergen sensitivities were unavailable for 12 children in the AR cohort (children who never developed CRS) who had allergy testing performed at another institution, and these 12 children were excluded from analyses that involved aeroallergen data.

Univariate logistic regression was performed for each predictor variable. Multivariate logistical analysis was performed by using all predictor variables that had $P < .10$ in univariate analysis. In the multivariate model, significant predictors were identified via backward elimination by using a P value cutoff of .100. Cross validation was performed through bootstrapping of the data set by using the *validate()* function from the *rms* package over 100 iterations. For each variable retained in the final model, a P value and a log-odds ratio were calculated. P values less than .05 were considered significant in the analysis of associations. The inclusion of predictor variables in the final multivariate model (as indicated above with the backward elimination approach) was confirmed independently with forward selection and stepwise selection approaches (implemented in the statistical software SAS [SAS Institute, Cary, NC]) by using the χ^2 goodness of fit to determine the optimal parameter combination in the final multivariate model.

Associations between the temporal progression to CRS and the same predictor variables used for logistic regression (described

in the Statistical analysis section) were determined with the Cox proportional hazard function `coxph()` in the survival package of R. Patients in the AR cohort were censored from the survival analysis at the last follow-up visit in which a diagnosis of AR (in the absence of CRS) was confirmed. The end point for patients in the AR-CRS cohort was the time when a diagnosis of CRS was documented. Univariate Cox proportional hazard regression was performed for each predictor variable. Multivariate Cox proportional hazards regression was then performed by using predictor variables with $P < .10$ in univariate analysis. In the

multivariate Cox proportional hazards model, significant predictors were identified via backward elimination by using a P value cutoff of .10.

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