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Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy

Aaron N. Pearlman, M.D.[*], **Rakesh K. Chandra, MD.**[*], **Dennis Chang, M.D.**[§], **David B. Conley, M.D.**[*], **Anju Tripathi Peters, M.D.**[#], **Leslie C. Grammer, M.D.**[#], **Robert T. Schleimer, Ph.D.**[#], and **Robert C. Kern, M.D.**[*]

[*]Department of Otolaryngology–Head and Neck Surgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois

[#]Department of Division of Allergy and Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

[§]Loma Linda University Sinus and Allergy Center, Department of Otolaryngology Head and Neck Surgery, Loma Linda University Medical Center, Loma Linda, California

Abstract

Background—The effect of comorbid conditions such as asthma and atopy on the severity of chronic rhinosinusitis (CRS) and the presence of nasal polyps (NPs) remains an area of investigation. We sought to elucidate the relationship among these entities.

Methods—The study population included 106 consecutive patients who were referred to a multidisciplinary, university-based allergy and sinus clinic that underwent computed tomography (CT) scan, skin-prick testing, and had CRS. Data were analyzed to determine Lund-MacKay score (LMS), presence of NPs, asthma status, and sensitivity to seven classes of aeroallergens.

Results—Skin tests were positive in 52 cases and negative in 54 cases. Although, there was no statistical relationship between LMS and atopic status in the entire group, among the asthmatic subgroup, mean LMS was greater in nona topic asthmatic patients than in atopic asthmatic patients. Asthmatic patients had a higher LMS than nonasthmatic patients ($p < 0.0001$). Asthmatic patients were more likely than nonasthmatic patients to have NPs (57.6% versus 25%; $p = 0.0015$), regardless of atopic status. Mean LMS was higher in NP patients compared with nonpolyp patients ($p < 0.0001$), independent of atopic status. Mean LMS was not affected by sensitivity to any particular allergen, with the exception of cockroach-allergic patients who were more likely to have an LMS of >10 ($p = 0.0236$) and had more severe maxillary sinus involvement ($p = 0.0391$).

Conclusion—These data indicate a strong relationship between CRS severity, as measured by LMS, and chronic airway inflammatory diseases, asthma, and NPs. The association between LMS and atopic status appears weak. The present study suggests that CRS is an inflammatory disease that occurs independently of systemic IgE-mediated pathways.

Address correspondence and reprint requests to Rakesh Chandra, M.D., Department of Otolaryngology–Head and Neck Surgery, Northwestern University Feinberg School of Medicine, 303 East Chicago Avenue, Searle 12-561, Chicago, IL 60611 rickchandra@hotmail.com.

This study has been approved by the Northwestern University Office for Research Institutional Review Board

Keywords

Allergy; asthma; atopy; chronic rhinosinusitis; computed tomography; eosinophil; epidemiology; Lund-MacKay score; nasal polyposis; staging

Rhinosinusitis is one of the most common medical complaints and affects nearly 31 million people annually in the United States.[1] The condition is characterized as chronic rhinosinusitis (CRS) if two or more symptoms persist for >12 weeks; symptoms include facial pain/pressure, purulent nasal discharge, nasal obstruction, and decreased sense of smell in the setting of chronic inflammation confirmed through endoscopy or radiographic studies.[2] Furthermore, it has recently been accepted that CRS is a heterogenous disorder comprised of two primary phenotypic presentations, clinically differentiated as either CRS with nasal polyposis (CRSwNP) or CRS without nasal polyposis (CRSsNP). Exact triggers for the inflammatory pathways at work in these conditions remain topics of intense investigation, and fungi,[3] staphylococcal superantigens,[4] and biofilms[5] have all been implicated. Although CRS is frequently viewed as having an allergic component, the role of systemic atopy in the promotion or maintenance of the chronic inflammatory state remains uncertain.

Computed tomography (CT) has been used to assess the degree and distribution of paranasal sinus inflammatory disease in CRS. Multiple staging systems have been devised to quantify disease severity, and among these schemes, the Lund-MacKay score (LMS) is the most widely used, displaying a high degree of interobserver reliability.[6] Intuitively, comorbid systemic atopy may be related to the extent of inflammatory burden in patients with CRS. These possibilities are supported by prior studies that suggest that CT scans in atopic CRS patients are more likely to manifest increased inflammatory changes.[7–9] In contrast, other authors have suggested that atopic status is weakly, if at all, associated with severity of CRS by CT.[10–12] The association between asthma and CRS is well known.[13] One investigation revealed that 74% of severe asthmatic patients and 70% of mild-to-moderate asthmatic patients had symptoms consistent with CRS, and symptom scores were greater in the severe asthmatic group.[14] However, the effect of asthma on the radiologic severity of CRS and the role of atopy in this relationship, continues to remain unclear. We attempt to further elucidate the relationship between systemic atopy and asthma on the radiologic severity of CRS in a tertiary referral population. Subgroup analysis was also performed to differentiate CRSwNP and CRSsNP patients.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Northwestern University. Between January 1, 2004 and December 31, 2006, 165 consecutive patients were prospectively enrolled into the Northwestern University Feinberg School of Medicine Sinus and Allergy Center Database. The Center is a multidisciplinary, tertiary care partnership between the Departments of Otolaryngology and the Division of Allergy and Immunology in the Department of Medicine. Inclusion criteria for the present study consisted of (1) having a diagnosis of CRS as defined by the American Academy of Otolaryngology–Head and Neck Surgery Task Force on Rhinosinusitis, (2) having a CT scan of the paranasal sinuses, and (3) skin testing for inhalant allergens. Patients under the age of 18 years were excluded. Overall, 106 of the 165 patients met the inclusion criteria for participation. Demographic data such as gender and age, in addition to a history of asthma, were acquired. Endoscopy was performed and the presence or absence of NPs was noted. LMS was rated by two otolaryngologists not involved in the direct care of the patients (A.N.P. and D.C.). In brief, the LMS assigns a score of 0, 1, or 2 to each sinus and a score of 0 or 2 for each

osteomeatal complex for a possible total score of 24. A score of 0 is assigned for a completely aerated sinus; a score of 1 is assigned for a partially opacified sinus; and a score of 2 is assigned for a completely opacified sinus. In reference to the osteomeatal complex, 0 is assigned if unobstructed and 2 is assignied if obstruction exists.

Each patient underwent skin-prick testing using lancets (Hollister-Stier, Spokane, WA) to tree pollens (elm, oak, ash, beech, cottonwood, hickory, maple, and box elder), grass pollens (blue, orchard, Bermuda, and timothy), weed pollens (ragweed giant and short), mold species (Aspergillus fumigatus, Dematiaceae, Penicillium, Alternaria alternate, Cladosporium herbarum, and *Helminthosporium sativum*), house-dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), cat hair, dog hair, feathers, and cockroach. A positive skin test response was defined as a wheal greater in size than that produced by the saline control of ≥3 mm. Histamine was used as a positive control. Subjects with allergic rhinitis had at least one positive skin reaction with the prick-puncture technique to the extracts. Intradermal skin testing was not routinely performed.

Data were analyzed to determine the effect of atopic status, asthma, and CRS phenotype on LMS. Further evaluation was conducted to asses the effect of atopic status and asthma on CRS phenotype. Finally, atopic patients were studied separately to determine if sensitivity to any particular allergen was associated with LMS or CRS phenotype. Statistical analysis was performed using χ^2-contingency, student's t, Mann-Whitney U, standard least squares, nominal logistic fit, and analysis of variance (ANOV A) testing, where appropriate. A value of $p < 0.05$ was considered statistically significant.

RESULTS

In this cohort of 106 patients, skin tests were positive in 52 (49%) patients (atopic) and negative in 54 (51%) patients (nona topic). Forty (38%) patients had CRSwNP and 66 (62%) patients had CRSsNP. Asthma status was unknown in 5 patients, who were excluded from analyses involving this variable. Among the remaining 101 patients, 33 (33%) had asthma. In the CRSsNP group, the prevalence of atopy was significantly greater in asthmatic patients than in non asthmatic patients (Fig. 1). Contrastingly, among the CRSwNP patients, the prevalence of atopy was similar between those with and without asthma.

When comparing atopic and non atopic patients, mean LMS was similar between groups (9.98 versus 10.01, respectively). In contrast, when comparing disease severity as a function of CRS phenotype, mean LMS was greater in CRSwNP patients compared with those with CRSsNP (15.2 versus 6.8, respectively; $p < 0.0001$). Mean LMS was also compared between asthmatic patients and nonasthmatic patients. This indicated that LMS was significantly greater in the asthmatic group (15 versus 7.5, respectively; $p < 0.0001$).

Multivariate analysis revealed that LMS was greater when the patient carried diagnoses of CRSwNP ($p < 0.001$) or asthma ($p < 0.001$), but positive atopic status was not a significant factor ($p = 0.35$). Further analysis was conducted to determine the effect of asthma in conjunction with atopy on LMS. ANOVA with *post hoc* testing revealed that mean LMS was greatest in nonatopic asthmatic patients, followed by atopic asthmatic patients, followed by nonasthmatic patients (Fig. 2). Similarly, we determined the effect of CRSwNP in conjunction with atopy on LMS. This showed that mean LMS was greater in patients with CRSwNP, but this association was independent of atopic status (Fig. 3).

Data were also analyzed to determine whether either atopy or asthma were associated with a diagnosis of CRSwNP in this sample. The prevalence of CRSwNP was similar between atopic and nonatopic patients (38% versus 37%). However, asthmatic patients were more likely to have CRSwNP (57.6%) than were nonasthmatic patients (25%; ($p = 0.0015$).

Multivariate analysis indicated that presence of CRSwNP was significantly associated with asthma ($p = 0.0019$) but not atopy ($p = 0.79$).

Among the atopic patients, mean LMS or presence of CRSwNP was not affected by sensitivity to any particular allergen, with one notable exception. Patients with cockroach allergy ($n = 19$) were more likely to exhibit an LMS of >10 (70.6%) compared with those without cockroach allergy (37.1%; $p = 0.0236$). When the LMS of each individual sinus was examined as a function of allergen sensitivity, the only significant association was that total maxillary sinus score (range, 0–4) was greater in patients with cockroach allergy than those without cockroach allergy ($p = 0.0391$).

DISCUSSION

The mechanistic relationships between atopic status, CRS phenotype, and radiological severity of disease have all been subjects of ongoing investigation. Systemic atopy has often been suggested as a likely predisposing condition for the development of CRS, and prior studies have supported an association between allergic status and degree of CRS. Newman *et al.* investigated the relationship between extent of disease on CT scan and asthma, allergy, and eosinophilia and concluded that asthma, IgE antibodies to specific inhalant antigens, and eosinophilia directly correlated with advanced disease.[7] Patients who were not atopic by radioallergosorbent test were found to have less significant inflammation by CT. Ramadan *et al.*[8] examined the relationship between radioallergosorbent test positivity and CT findings, also using LMS. This sample population of 25 nonatopic and 17 atopic patients revealed that mean LMS was significantly greater in the latter group ($p = 0.03$). In this cohort, asthma was not a predictor of higher LMS.[8] Finally, increased skin end point titration scores have also been correlated to advanced CT stage ($r = 0.42$; $P < 0.01$).[9]

The observations reported here suggest that atopy may be associated with asthma in the CRSsNP subset, but in contrast to the aforementioned reports, atopy was not associated with advanced LMS in the present series. We also observed no correlation between atopy and the CRSwNP phenotype, a finding that has been reported previously by Banerji *at al.* In a cohort of 47 CRS patients who underwent skin-prick testing, there was no statistical association between systemic atopy and CRSwNP.[12] Our findings do contrast somewhat with those of Hamilos,[13] who has observed increased incidence of house-dust mite allergy in CRSwNP patients. This suggests that some forms of atopy may be implicated in subsets of CRSwNP patients, despite the lack of association observed when these patients are aggregated. Further study is necessary to elucidate possible phenotype subtleties within the CRSwNP population to determine in which patients atopy may be an underlying factor.

As suggested by Hamilos,[13] we also observed that the presence of asthma was associated with the CRSwNP phenotype, and in the present series, both of these factors were correlated with elevated LMS. Other investigators have corroborated these findings. Settipane reported a series of over 2000 patients with allergic and nonallergic asthma in an effort to estimate the incidence of NPs in these groups. It was found that NPs were more common in nonallergic asthmatic patients versus allergic asthmatic patients (13% versus 5%; $p < 0.01$).[10] Robinson *et al.*[11] recently described similar findings in a cohort of 193 CRS patients in which the incidence of atopy was 30%. In that study, higher LMS correlated with the presence of NPs ($p = 0.02$), as was observed in the present investigation. Although they observed that mean LMS was slightly greater in atopic patients than was observed in nonatopic patients (14.2 versus 12.3, respectively; $p = 0.05$), significance was lost when the cohort was stratified into CRS patients with and without NPs. It was concluded that atopic status did not significantly affect either group in relation to quality of life or symptoms and had only a modest effect on CT findings.[11]

Consideration was given to whether any individual allergens could be related to LMS or CRS phenotype. The only significant association was that patients with a cockroach allergy were found to have an elevated mean LMS (above 10). Speculation has been made that atopic patients will have increased edema of the middle meatus and should thus have increased propensity for obstruction of sinuses that drain into this space (maxillary, anterior ethmoid, and frontal) and the osteomeatal complex. However, cockroach was the only allergen that could be correlated to increased inflammation in any particular sinus, where total maxillary sinus score was significantly elevated in those with a cockroach allergy. Cockroach, a perennial allergen, may have the potential to access the maxillary sinus more easily than other antigens and thus cause increased inflammation. This may be a function of its particle size or other unknown property. However, this finding must be interpreted cautiously because it could be a result of sampling error. It should also be noted that CRSwNP phenotype was not associated with sensitivity to any individual allergen. One limitation of the present report is that available data precluded correlation of the variables studied with *symptomatic* severity of disease. It is thus possible that presence of allergic rhinitis may impact overall degree of symptoms despite lack of demonstrated effect on radiological disease severity.

In this study, we have shown that presence of asthma, rather than atopic status, is the key predictor of increasing severity of radiologic disease and CRSwNP phenotype, which has been corroborated by prior reports.[12,15] The incidence of asthma in our cohort was 33%, which is similar to prior studies in a tertiary sinus and allergy setting that have estimated the incidence of asthma to be 23% in patients with CRS versus 5% in the general population.[16] Asthma and CRS both reflect chronic inflammatory processes involving the airway mucosa and studies have indicated a similar pathophysiological process in subgroups of patients with CRS and asthma. Specifically, tissue in CRS patients with NPs exhibits increased degree of eosinophilic infiltrate compared with that from CRS patients without NPS.[17] Similarly, in asthma, the inflammatory infiltrate is composed of eosinophils, in addition to mast cells and $CD4^+$ T lymphocytes.[18] A possible mechanism for the relationship between severe CRS and asthma has been proposed by Bachert *et al.* where the production of inflammatory cytokines induces bone marrow to up-regulate eosinophils, mast cells, and basophils, which ultimately migrate to the airway mucosa and cause a reactive inflammatory response.[19]

Furthermore, it has been suggested that local tissue-specific IgE production may play an important role in patients with NPs who have negative skin testing. Total local concentration of IgE in NPs has been found to be significantly elevated in CRSwNP. Also, the up-regulation of IgE to specific allergens including *Staphylococcus aureus* enterotoxins, which act as superantigens up-regulating the production of polyclonal IgE antibodies, has been observed.[4] Thus, even in the absence of a significant relationship between systemic allergic phenotype and CRS or LMS, local allergic response may play an important role in CRSwNP. These data suggest that CRS may reflect a *local* rather than systemic response, offering insight into why skin test results poorly correlate with disease severity.

CONCLUSION

These data show a strong relationship between the radiological severity of CRS and asthma, both of which are manifestations of chronic airway inflammatory disease. Asthma was also associated with the CRSwNP phenotype, which also appeared to contribute to overall radiological disease severity. The association between systemic atopic status and CRS severity appears weak in this sample. In this series, the only class of common allergens that was associated with CRS severity was cockroach. The present study suggests that CRS is an

inflammatory disease of the respiratory mucosa that occurs independently of systemic IgE-mediated pathways.

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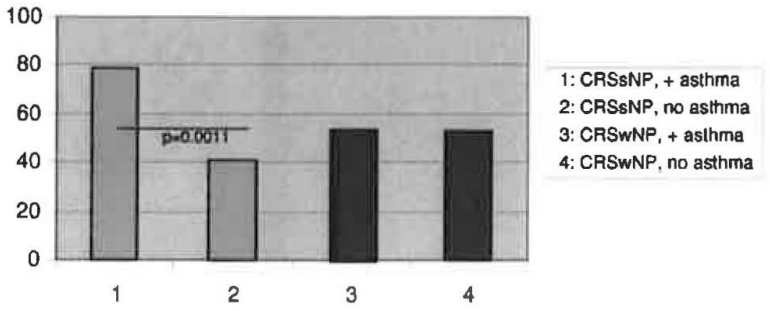

Figure 1.

Percent of patients with positive skin testing as a function of chronic rhinosinusitis (CRS) phenotype and asthma status. Among CRS without nasal polyposis patients, atopy was more prevalent in those who had asthma (1 and 2). Among CRS with nasal polyposis patients, atopy was similar between asthmatic and nonasthmatic patients (3 and 4).

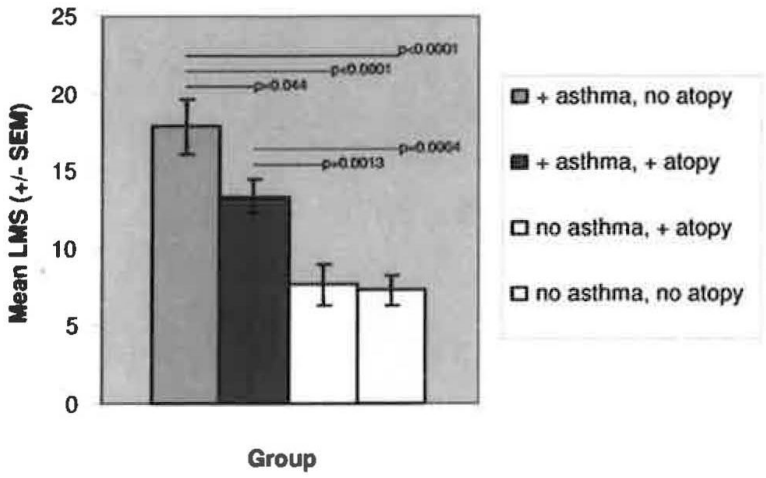

Figure 2.

Mean Lund-MacKay score (LMS) was greatest in nonatopic asthmatic patients followed by atopic asthmatic patients. Nonasthmatic patients exhibited a lower mean LMS, and this observation was regardless of atopic status.

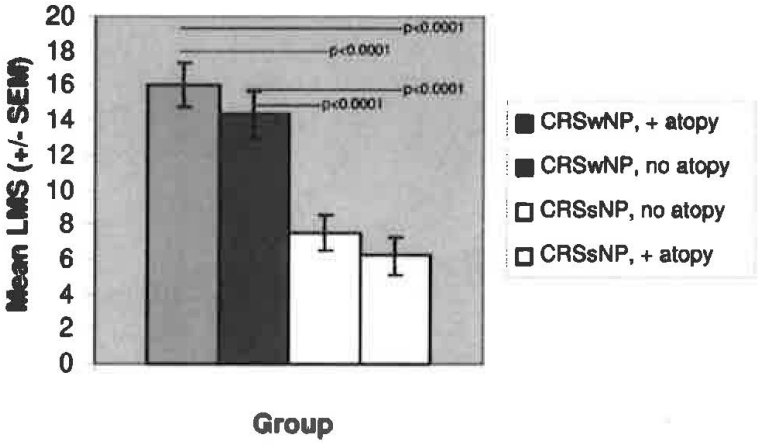

Figure 3.
Mean Lund-MacKay score (LMS) was greater in polyp patients with and without atopy. Nonpolyp patients had lower mean LMS, regardless of atopic status.