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The Relationship Between Allergy and Chronic Rhinosinusitis

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Objective: To summarize the current evidence regarding a relationship between chronic rhinosinusitis (CRS) and allergy.
Methods: Literature review.
Results: Despite frequent assumption of an association between CRS and allergy the relationship between these entities remains poorly defined. Certain CRS entities, however, have demonstrated a strong association with allergy—namely allergic fungal rhinosinusitis and central compartment atopic disease.
Conclusion: Studies are heterogeneous and largely retrospective in design with inconclusive evidence for an association between CRS and allergy. Knowledge of CRS endotypes is important in order to understand which entities may or may not be associated with allergy.
Key Words: Allergy, atopy, chronic rhinosinusitis, nasal polyposis, sinusitis.
Level of Evidence: 5

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory condition affecting the nose and paranasal sinuses that, by previously defined criteria, lasts 12 weeks or more.[1,2] The disorder is commonly divided into two subtypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). However, there is increasing evidence that within these broad phenotypes, several endotypes exist, which are being further elucidated and increasingly discussed.

Despite growing knowledge regarding CRS, its pathogenesis is not well established. Furthermore, various etiologies may contribute to the development of CRS (ie, alterations in microbiome composition, epithelial barrier dysfunction, defects in innate immunity, biofilm formation, congenital factors, and others), and inflammatory patterns vary widely. Therefore, the treatment of CRS is often challenging. As the overall CRS disease process is inflammatory in nature, significant study is directed toward determining which factors may incite and propagate the inflammation.

Allergic diseases, especially IgE-mediated inflammatory processes such as allergic rhinitis, are commonly thought to be an inciting factor in the development of CRS or a comorbidity/associated factor for the propagation of the CRS disease state. The rationale is that allergy-induced mucosal inflammation may lead to sinus ostial obstruction, and thus, secondary infection. Although an association of allergy with CRS has been previously studied, the relationship remains poorly understood.

This review summarizes the current evidence regarding a relationship between allergy and CRS, taking into account different CRS subtypes and allergens. We performed a literature review using the PubMed database. Search terms included combinations of the following phrases: “chronic rhinosinusitis”, “sinusitis”, “allergy”, “atopy”, and “polyposis”. Each reference section was further reviewed to identify additional publications.

ASSOCIATION BETWEEN ALLERGY AND CHRONIC RHINOSINUSITIS: SUMMARY

Several studies have sought to better understand the relationship between allergy and CRS with and without nasal polyposis. The most robust systematic review evaluating this relationship was performed by Wilson et al.[3] Twenty-four articles were included in this review. Studies which did not delineate CRSwNP or CRSsNP status were excluded.

Eighteen studies were identified which analyzed an association between allergy and CRSwNP.[3] Ten demonstrated a positive association between these two entities, whereas seven did not. One study showed equivocal findings. Since the Wilson review in 2014, Li et al. published an additional study which demonstrated no association between allergy and disease severity in patients with CRSwNP.[4] Regarding a relationship between allergy and CRSsNP, nine studies were identified in the Wilson review. Four showed an association between allergy and CRSsNP; five studies did not demonstrate an association. Thus, nearly an equal number of studies supported or refuted an association of allergy with both CRSwNP or CRSsNP. Given these findings, Wilson et al. and the

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International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis concluded that the aggregate level of evidence was level D linking allergy to either CRS subtype.[3,5] Allergy testing and treatment in the CRS patient are suggested as an option given possible benefit with little harm.

Overall, there is conflicting data regarding an association between allergy and CRSwNP or CRSsNP. There is however evidence for an association with certain allergen types, ie. perennial allergens, and certain CRS subtypes, including allergic fungal rhinosinusitis (AFRS) and the more recently described, central compartment atopic disease (CCAD). These will be specifically addressed later in this review.

TABLE I.
Association Between Allergy and Chronic Rhinosinusitis: Overview of the Evidence.

Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)	• Equivocal evidence regarding an association with allergy
Chronic Rhinosinusitis without Nasal Polyposis (CRSsNP)	• Equivocal evidence regarding an association with allergy • Few studies specifically evaluating CRSsNP cohort
Allergic Fungal Rhinosinusitis (AFRS)	• Strong evidence regarding an association with allergy • Weak evidence for role of immunotherapy
Central Compartment Atopic Disease (CCAD)	• Strong association with inhalant allergy • Limited number of studies as entity only recently described
Allergen Type (Perennial vs. Seasonal)	• Suggestion of an association between CRSwNP/CRSsNP and perennial allergens • Weak evidence for an association between CRSwNP/CRSsNP and seasonal allergens
Role for Immunotherapy (IT)	• Weak evidence for role of immunotherapy limited by number and quality of studies • More research needed for CRS subtypes including AFRS and CCAD

CONCERNS WITH THE CURRENT LITERATURE: DEFINITIONS AND DIAGNOSIS

In studies that have examined a relationship between allergy and CRS, the definitions of allergy and CRS often vary across studies, at times making direct comparisons difficult. Additionally, allergy testing methodology can also vary which may lead to varied classification of allergen sensitization and/or clinical allergic manifestations across studies.

Definitions

The European Academy of Allergy and Clinical Immunology (EAACI) Task Force published "A Revised Nomenclature for Allergy" to better clarify terminology used to describe allergy.[6] *Hypersensitivity* refers to objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons; hypersensitivity may be allergic or non-allergic. *Allergy* is a hypersensitivity reaction initiated by a foreign antigen. Typical allergic rhinitis, or nasal allergy symptoms, are associated with IgE-mediated reactivity to an inciting allergen. However, allergy does not have to be IgE-mediated. For example, reactions mediated by lymphocytes, and not antibodies, may also be considered allergic, such as contact dermatitis. *Atopy* is a tendency to become sensitized and produce IgE antibodies in response to ordinary exposures. Thus all atopic reactions are considered allergic, but not all allergic reactions are considered atopic.

Diagnostic criteria for CRSsNP includes at least 12 weeks of two or more of the following symptoms: nasal drainage, nasal congestion, hyposmia/anosmia or facial pressure/pain, and objective evidence of inflammation visualized on either computed tomography scan (CT) or endoscopy. Diagnostic criteria for CRSwNP are the same for CRSsNP, but with the addition of nasal polyposis.[1,2] A limitation within the literature is that although considered to be distinct clinical and pathological entities, studies examining the relationship between allergy and CRS often included patients with and without polyposis in the same cohort.[7,8] Furthermore, evidence demonstrates that even amongst patients with polyposis, certain CRS variants may be more closely associated with allergen exposure, ie, AFRS. In studies that examine the relationship between allergy and CRSwNP, it is often not clarified whether specific endotypes like AFRS are included within or excluded from the nasal polyposis cohort, thus potentially skewing the analysis in one direction or the other.

Diagnosis

Accurate diagnosis of allergen sensitization is paramount to identify atopic patients. The primary methods to determine IgE-hypersensitivity are skin testing (skin prick testing, intradermal skin testing, and blended techniques) and in vitro serum allergen-specific IgE testing. Among studies, the chosen technique varies and the rationale is often not described.[9,10] This poses a potential problem as there is some discordance between skin and serum specific IgE testing. In fact, there has been a prior recommendation to use both testing modalities when conducting research in order to prevent misdiagnosis.[11] Furthermore, there is evidence that systemic allergy testing may not always reflect nasal pathophysiology. In a subset of patients, systemic allergy testing may be negative but locally-present IgE in the sinonasal cavity may be present, a condition that has been referred to as local allergic rhinitis or "entopy."[12] To illustrate this concept, a systematic review by Hamizan et al.[13] compared local nasal allergen reactivity with systemic reactivity in rhinitis patients. They found local reactivity in 26.5% of patients previously considered non-allergic. In these patients, detection of local nasal allergen-specific IgE was obtained via a nasal allergen provocation test, a test seldom performed within the aforementioned literature.

Despite these limitations, trends and conclusions can be drawn from prior studies which will be discussed below. An overview of the evidence for an association between chronic rhinosinusitis and allergy can be found in Table I.

ASSOCIATION BETWEEN ALLERGY AND CHRONIC RHINOSINUSITIS: CRSwNP AND CRSsNP

Chronic Rhinosinusitis With Nasal Polyposis

Elevated IgE, mast cell degranulation, eosinophilia and a helper T-cell type 2 (Th2) cytokine profile within the sinonasal mucosa is often seen in CRSwNP.[14] These features may be seen in allergic conditions as well. Thus an association between these two entities has frequently been assumed given their pathophysiologic overlap. It would also be expected that nasal polyposis would be more prevalent in patients with allergy and conversely that allergy would be more prevalent in patients with nasal polyposis. However, neither has been definitively demonstrated in the literature.

Most atopic patients do not develop nasal polyposis. A study performed by Caplin et al.[15] found that in 3000 atopic patients only 0.5% had nasal polyposis. This prevalence of nasal polyposis is similar to the general population. Whether patients with CRSwNP have a higher prevalence of allergies has also been studied, but conflicting data exists. In support of a higher prevalence of allergies in CRSwNP patients, Munoz del Castillo et al.[9] reported increased rates of positive skin prick testing (SPT) among CRSwNP patients compared to controls. Tan et al.[10] also found that the median number of positive SPT was higher in CRSwNP than in CRSsNP or allergic rhinitis patients, yet these results did not reach statistical significance.

Other studies have demonstrated no evidence of a relationship between allergy and CRSwNP. Bonfils et al.[16] found that allergy had no effect on any outcome measure in patients with CRSwNP. Gorgulu et al.[17] showed that the prevalence of allergy was 25% in patients with CRSwNP compared to 28% in controls, and that allergy was not a risk factor for developing nasal polyposis. Erbeck et al.[18] demonstrated no effect of allergy on disease severity. They compared allergic and non-allergic patients with nasal polyposis and found no association between the presence of allergy by SPT on polyp size, CT opacification, symptom scores, or recurrence. Thus, conflicting data exists as to whether allergy impacts the development or course of CRSwNP.

Chronic Rhinosinusitis Without Nasal Polyposis

Fewer studies have examined the relationship between CRSsNP and allergy. In addition, older studies were often not specific, often using the term "chronic sinusitis" to include both patients with and without polyposis. One study, which specifically looked at patients with CRSsNP, found that patients with ragweed sensitivity had a significantly higher eosinophil count on maxillary sinus lavage during ragweed season than during other times of the year.[19] They concluded that pollen exposure leads to sinus inflammation. Other studies have shown that allergic patients were more likely to have abnormal sinus plain film[20] or CT imaging.[21] These studies suggest that allergic patients may have a higher disease burden when compared to their non-allergic counterparts. However, several other studies demonstrated no association of CRSsNP with allergy. Gelincik et al.[22] found that CRS was equally prevalent in patients with allergic and non-allergic rhinitis. Therefore, conflicting data also exists as to whether allergy impacts the development or course of CRSsNP.

SPECIFIC SUBTYPES OF ALLERGY AND RHINOSINUSITIS DEMONSTRATING AN ASSOCIATION

Type of Allergen

Several studies have demonstrated an increased prevalence of perennial, rather than seasonal, allergies in CRS patients. Gutman et al.[8] showed perennial allergy to have a statistically significant association with CRS, most prominently mold and house dust mites. However, they did not distinguish polyposis status. Among CRSwNP patients, Houser and Keen[23] demonstrated 56.4% to have sensitivity to at least one perennial allergen compared to approximately 5% in the general population. This was further reinforced by other studies.[24,25] Among CRSsNP patients, Berrettini et al.[21] found an association between patients with perennial allergic rhinitis and CRSsNP. They found CT evidence of sinusitis in 68% of allergic patients and only 33% of controls. Overall, these studies suggest that duration of allergen exposure may be associated with CRS with and without polyposis and may affect progression of disease.

Allergic Fungal Rhinosinusitis

AFRS is a noninvasive, recurrent subset of CRSwNP that is associated with IgE-mediated hypersensitivity to fungal allergens.[26] In 1994, Bent and Kuhn published five major criteria to establish the diagnosis of AFRS, one of which is type I hypersensitivity confirmed by history, skin testing or serology. Therefore by definition, all patients with AFRS have allergy. Manning et al.[27] published one of the first reports regarding the role of fungal allergen hypersensitivity in AFRS. They compared eight patients with culture-positive *Bipolaris* AFRS to ten control subjects and found *Bipolaris*-specific IgE and IgG antibodies in the AFRS patients. This was confirmed in a study by Saravanan et al.[28] which demonstrated that greater than 90% of patients with AFRS had a type I hypersensitivity reaction observed via skin testing. Hutcheson et al.[29] showed that AFRS patients have elevated serum and fungal-specific IgE compared to other CRS variants and normal controls. These studies reinforce the role of allergy in AFRS patients.

Interestingly, while allergy does appear to play a role in AFRS pathogenesis, and likely perpetuation, studies that have examined the role of allergen-specific immunotherapy in the treatment of AFRS have a relatively low level of evidence. In 2014, Gan et al. [30] performed a review of the medical management of AFRS and found 5 studies examining the benefit of allergen immunotherapy in the treatment of AFRS. The aggregate level of

evidence was C, and this treatment modality is recommended as an option. Allergen immunotherapy in the treatment of CRS and AFRS is further discussed later in this review.

Central Compartment Atopic Disease

Central compartment atopic disease (CCAD) is a recently described CRS variant strongly associated with allergy. Originally published in 2014, White et al.[31] described polypoid and edematous changes of the middle turbinate in which all twenty-five patients included tested positive for inhalant allergy. The proposed etiology was that the anterior aspect of the middle turbinate is exposed to inhalant allergens via nasal airflow. These findings were confirmed by Hamizan et al. [32] using a larger sample size. Brunner et al. [33] demonstrated a distinction between central disease and diffuse nasal polyposis, with a higher association of allergen sensitization in patients with isolated middle turbinate changes. A more advanced form of this inflammatory disease was later described by DelGaudio et al.[34] whereby other central structures including the posterior-superior nasal septum, middle turbinates, and superior turbinates were involved. In addition, a central opacification of the paranasal cavities with peripheral clearing is often seen. In this study all 14 patients had positive allergy testing. Hamizan et al.[35] evaluated radiologic findings associated with CCAD, and found that a central pattern of mucosal disease had a higher association with allergy. Overall these studies suggest that long-term management of these patients would benefit from environmental allergy testing and treatment. However, in light of the fact that this is a newly described entity, more evidence is needed regarding the etiology and clinical course of this CRS subtype.

ROLE FOR IMMUNOTHERAPY

Whereas there is a strong recommendation for allergen immunotherapy (IT) in patients with allergic rhinitis (AR),[5] the role for IT in the treatment of CRS remains less clear. A systematic review performed by DeYoung et al.[36] looked at sinusitis-specific outcomes in CRS patients who underwent IT. Seven studies were ultimately included which demonstrated symptom reduction in the short-term, however this conclusion was deemed weak and limited by the number and quality of studies. The paper also questioned the degree to which sinus-specific outcomes can be separated from AR outcomes, and that overall symptom improvement may be due to AR rather than CRS improvement. Current CRS treatment guidelines recommend allergy testing and treatment as an option.[1]

The role of IT specifically for the treatment of AFRS has also been examined. Although there is a lack of randomized, controlled studies, some small studies have shown benefit from IT for AFRS. Mabry et al.[37] compared two cohorts of AFRS patients treated with the same regimen except that one cohort received IT. The IT cohort demonstrated improved quality of life and ultimately did not require systemic corticosteroids. Folker et al.[38] demonstrated decreased severity in patient symptoms who received IT. However, a more recent evidence-based review by Gan et al. concluded, based on a limited number of studies, that there was an equal degree of benefit and harm, and that IT should only be considered as an option for AFRS.[30]

The role of immunotherapy in CCAD has not yet been studied.

CONCLUSION

Overall, the association between allergy and CRS remains debatable when patients are subtyped by broad phenotypic categories such as CRSwNP and CRSsNP. There is suggestion of a relationship between patients with certain CRS variants and perennial allergen sensitivities. In addition, specific subtypes of CRS, such as AFRS and CCAD, appear to have a stronger relationship to allergy. It is likely that with better defined allergy and CRS categorization, we will be able to better delineate the relationship between allergy and specific CRS endotypes in the future.

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