



Updates to the Current Understanding of the Relationship Between Allergy and Chronic Sinusitis

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Abstract

Purpose of Review To examine the relationship of chronic rhinosinusitis (CRS) and atopic disease.

Recent Findings CRS with nasal polyps (CRSwNP) has been shown to be associated with high aeroallergen sensitivity and local allergic response, but with no difference in imaging, symptomatic severity, or disease recurrence rates in atopic vs. non-atopic individuals. There is conflicting evidence for CRS without nasal polyps (CRSSNP) with regard to the relationship with atopic disease. There may, however, be differential molecular profiles between atopic and non-atopic patients with CRSSNP.

Summary There is no consensus as to whether atopic disease is related to CRS. Recent studies have shown that atopic disease may be implicated in pathogenesis, but may not contribute to clinical severity. It should, however, be noted CRS likely has multifactorial etiologies. Finally, specific subtypes of CRS, such as central compartment atopic disease (CCAD), are likely atopy driven and allergic management should play a key role in treatment of these patients.

Keywords Rhinosinusitis · Sinusitis · Allergy · Polyp · Atopy · Allergic · Allergic rhinitis · Chronic rhinosinusitis · Nasal polyp

Introduction

Chronic rhinosinusitis (CRS) is defined as sinonasal inflammation lasting for more than 12 weeks, accompanied by nasal obstruction/congestion, nasal drainage, facial pain or pressure, and poor sense of smell [1, 2]. On the basis of clinical findings, CRS can be further classified into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSSNP). CRSwNP is diagnosed upon visualization of polyps in the nose [2] in addition to the diagnostic criteria of CRS. In the general population, it is estimated that the prevalence of CRS is 5–12% and costs \$12.8 billion in the USA yearly [3, 4]. Allergic rhinitis is defined as nasal

symptoms associated with exposure to an aeroallergen to which the patient is sensitized and is a type I IgE-mediated hypersensitivity reaction. The prevalence of allergic rhinitis in the general population is 10–30% and continues to increase worldwide [5]. Allergic sensitization (positive specific aeroallergen testing regardless of the presence of symptoms) is more common than allergic rhinitis, with an estimated prevalence of 44.6% in the USA [6].

CRS itself is a heterogeneous disease rather than a single entity, encompassing several phenotypes and endotypes with unique factors causing progression of disease and increased morbidity [2]. The association of allergy and CRS is one such factor that is poorly understood [7]. Some studies suggest that allergy predisposes to and propagates CRS, while other studies refute this association [8]. This review seeks to summarize and interpret the literature discussing the association between allergy and CRS in order to add to the understanding of potential modifiable factors that may decrease morbidity to improve symptomatic control in CRS. The authors have followed general nomenclature and separated CRS groups into those with nasal polyps (CRSwNP) and those without nasal polyps (CRSSNP). In addition, the authors have added the relatively newly defined category of central compartment atopic disease (CCAD), an etiology of CRS which seems particularly related to atopic disease.

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Allergy and Chronic Rhinosinusitis with Nasal Polyps

Support for the Relationship Between Chronic Rhinosinusitis with Polyps and Allergy

There are a substantial number of papers demonstrating a relationship between CRSwNP and allergic disease. Some prior studies have found that patients with CRSwNP have higher mean number of positive allergy tests than CRSsNP patients and control rhinitis patients, with the majority being positive for multiple allergens [9, 10]. Furthermore, an association between nasal polyps and perennial allergen sensitization has been reported [10–12]. The suggestion is that perennial sensitization and chronic exposure to allergens in these patients may cause or contribute to the formation of nasal polyps due to the chronic inflammation. The most common allergen sensitizations in some of these studies were found to be *Candida* species and house dust mites on skin prick testing and intradermal skin tests [12, 13].

Traditionally, allergic rhinitis has been defined as an immediate type I hypersensitivity, with atopy involving systemic production of immunoglobulin E (IgE) antibodies and eosinophilic proteins. The term “entopy” or “local allergic rhinitis” has recently been used to describe a local increase in IgE load and inflammatory reaction in non-atopic individuals [14, 15]. This hypothesis is supported by prior studies which have shown that there is a robust polyclonal IgE response to cockroach and plantain antigens in CRSwNP sinus and turbinate tissue which is not found in CRSsNP and healthy controls. There was no difference in total IgE levels in sinonasal tissue between the three groups [16]. This suggests that local allergic responses, whether to aeroallergens or pathogens, may drive polyp formation in some patients. Similarly, Cheng et al. describe a cohort of CRSwNP patients who were found to have no significant elevation in total serum IgE or eosinophilic proteins; these patients did, however, have significant elevations in allergen specific IgE in local sinonasal tissue. This suggests that local allergy, rather than systemic allergy, may play a role in CRSwNP [15]. Furthermore, previous studies describe greater improvement in sneezing, nasal peak flow, and overall symptom severity with budesonide therapy in non-allergic CRSwNP patients than allergic CRSwNP patients. Kirtsreesakul et al. suggest that this is because of a local, intrinsic allergic response in atopic CRSwNP patients with allergies which is refractory to local therapy and inflammatory control [17].

Yacoub et al. note that patients with CRSwNP have higher rates of allergic rhinitis and asthma than control groups and sought to understand the mechanism of this association. They found that patients with recurrent CRSwNP had increased lower airway eosinophilic activity, circulating IgE, and were more likely to have atopic disease, determined by skin prick

testing. Additionally, it was noted that lower airway eosinophilic activity was significantly decreased after functional endoscopic sinus surgery (FESS). Given these findings, they proposed the hypothesis that allergic reactions occurring at the level of the upper airway propagate lower airway inflammation. This subsequently contributes to comorbid asthma in CRSwNP [18].

Finally, it has been previously proposed that food allergy may be related to CRSwNP, with these patients having higher rates of food sensitivity in some studies, and often having multiple food sensitizations, which were much less common in the non-CRSwNP groups [19, 20].

Evidence Against an Association Between Chronic Rhinosinusitis with Polyps and Allergy

While several studies have shown findings in support of allergy correlating with CRSwNP, other studies have found no association. Mortuaire et al. show no statistically significant difference between allergic and nonallergic CRSwNP patients in serum or local concentrations of IgE, IgA, IL-5, IL-9, and eosinophilic proteins, suggesting that the inflammatory profile in CRSwNP is independent of atopic status. Furthermore, they showed no impact of allergen sensitization on nasal polyp size or Lund-Mackay sinus CT scoring [21]. This is in keeping with other literature which demonstrated no difference in Lund-Mackay scores, symptom severity scores, or need for revision surgeries in atopic and non-atopic CRSwNP patients [22, 23].

Furthermore, when comparing patients with primary and recurrent CRSwNP, Li et al. found that there were no statistically significant differences in Lund-Mackay scores, total serum IgE, eosinophilic proteins, or in vitro allergy testing results. There was also no difference in polyp recurrence rate, symptom scores, or Lund-Mackay scoring in patients with proven atopic disease vs. patients without atopic disease, suggesting that allergy does not play a role in recurrent disease or symptomatic severity of CRSwNP [24]. Similarly, Guo et al. report higher mean baseline eosinophil count and proportion of total white blood cell count in patients with multiple recurrences of disease. There was, however, no statistically significant difference between atopic and non-atopic cohorts in serum eosinophil and white blood cell counts, and atopic and non-atopic patients also had similar rates of disease recurrence [25].

Finally, Mady et al. demonstrate that CRSwNP patients with negative allergy testing had significantly more exposure to air pollutants than atopic CRSwNP patients suggesting that there are extrinsic modifiers and other environmental factors in the development of CRSwNP in non-atopic individuals. This emphasizes the multifactorial etiology and diverse presentation of CRSwNP in allergic and nonallergic patients [26].

Adding to the food allergy discussion, Teles et al. studied serum IgG and IgE to common food allergens in CRSwNP patients and found that there was no significant elevation in either. They demonstrate a lack of relationship between IgE and IgG mediated food allergy in development of CRSwNP [27]. Furthermore, Al-Qudah et al. show no significant difference in food sensitivities in CRSwNP and CRSsNP patients with medically resistant disease [28].

Allergy and Chronic Rhinosinusitis Without Polyps

Support for the Relationship Between Chronic Rhinosinusitis Without Polyps and Allergy

The current understanding of the association between CRSsNP and allergy is more limited as fewer studies have examined this classification of CRS specifically. Similar to CRSwNP patients, though, Wang et al. found that there was no difference between atopic and non-atopic CRSsNP patients with respect to symptom severity or radiologic involvement. They did find, however, that atopic CRSsNP had higher total serum IgE and eosinophil load than non-atopic CRSsNP patients. Furthermore, these patients were found to have increased sinonasal mucosal eosinophils. With the use of differentiated inflammatory markers, they were able to discern between a Th1 and Th2 response and found that there was an increase in the Th2 response in the atopic cohort that was not seen in the non-atopic cohort. Given this unique inflammatory response, they suggested a new classification of CRSsNP, differentiating between atopic and non-atopic disease that may require therapy targeted toward specific inflammatory responses [29]. Berrettini et al. and Kirtsreesakul et al. also demonstrated an increase in sinus radiologic findings in patients with atopic disease compared to those without atopic disease, suggesting that allergic inflammation contributes to sinus opacification on imaging [30, 31]. It is important to note here that while several studies in the CRSsNP population have noted increased severity on imaging, the same findings have not been seen in CRSwNP populations, as demonstrated in the aforementioned studies.

In a study by Baroody, et al., the authors examined sinonasal symptoms and eosinophil counts in the sinuses with and without allergen exposure via quality of life questionnaires and sinus lavage in patients with ragweed allergies. The investigators found that symptoms worsened with exposure and that there were more eosinophils in the sinuses and nasal cavity in season with ragweed, suggesting direct sinus inflammation attributable to atopic disease [32]. In addition, it has been shown that in non-atopic CRSsNP patients, while there is no significant increase in total B cell populations in sinonasal tissue or peripheral blood, there is, however, a

higher proportion of IgE plasmablasts, responsible for the eventual formation of IgE and propagation of the allergic response [33].

Evidence Against an Association Between Chronic Rhinosinusitis Without Polyps and Allergy

While there is some evidence which alludes to an association between CRSsNP and allergy, there is also a body of literature arguing against an association. Lending to this debate, prior studies have shown no significant increase in allergy sensitivity in CRSsNP when compared with controls [9]. Derycke et al., in contrast to Wang et al., found that serum T cell profiles in patients with CRSsNP are similar to those of control patients. As such, they propose the hypothesis that CRSsNP is not an allergic inflammatory process but is rather due to sinonasal remodeling from other factors [29, 34]. Konig et al. found similar results, showing that inflammatory markers in sinonasal secretions from patients with CRSsNP had similar composition to control samples [35]. There is also the potential that environmental irritants contribute to this sinonasal remodeling. It has been shown that higher air pollutant exposure is correlated with higher SNOT-22 symptom severity scoring, regardless of allergy status in CRSsNP. This suggests a role for environmental factors, rather than allergy contributing to disease etiology and severity [26•].

On the clinical side, papers have demonstrated a lack of evidence for a significant role for atopic disease in CRS. Robinson et al. found in a group of nearly 200 CRS patients that atopy was not associated with revision surgery and had only small impacts on symptom scores, although they did find that atopic patients overall had higher Lund-Mackay CT scores [23]. Similarly, another study demonstrated that in patients with allergic rhinitis vs. nonallergic rhinitis, CRS symptom scores and CT scores were actually higher in the non-atopic group, leading them to conclude that atopy was not a predisposing factor in the development of CRSsNP [36].

Central Compartment Atopic Disease

Central compartment atopic disease (CCAD) is a newly described entity involving primarily inflammation of the central portion of the nasal cavity with peripheral sparing of the lateral portions of the sinuses. It is an inflammatory polypoid condition involving the middle turbinate most commonly, and less frequently the nasal septum, and superior turbinate. This results in middle meatus obstruction and sinonasal findings in advanced disease. It is closely related to inhalant allergy deposition and inflammatory changes causing increased swelling and obstruction [37].

Marcus et al. note significant correlation between known atopic disease and CCAD. They suggest that the nose acts as a

filtration system, with inhalant allergens being more likely to deposit at the middle turbinate, septum, and superior turbinates [37].

Clinical manifestations of CCAD include symptoms of nasal obstruction or congestion, with or without allergic symptoms such as itching nose/eyes and sneezing. On nasal endoscopy, patients are likely to have middle turbinate edema or polypoid changes, with advanced cases having significant polypoid changes that can mimic nasal polyps and sinus obstruction extending to the medial ethmoid region and maxillary sinus. In these cases, advanced disease is due to obstruction, rather than sinus mucosal changes due to inflammation [38•]. Nasal endoscopy findings in CRSwNP and CCAD can be found in Fig. 1.

Hamizan et al. describe imaging changes seen in CCAD. They note lower Lund-Mackay scores overall on CT than in CRS patients. Specific CT findings include soft tissue density in the central nasal cavity. Sinus involvement is seen in more advanced disease but tends to be centrally limited mucosal thickening and polypoid changes, with no or minimal sinus roof or lateral wall involvement [39].

Brunner et al. suggest that polypoid changes of the middle turbinate, as seen and exemplified in CCAD, is a clinically distinct disease process from CRS with no correlation in incidence. They found that CCAD is also heavily associated with allergic rhinitis. Therefore, they suggest alternative treatment

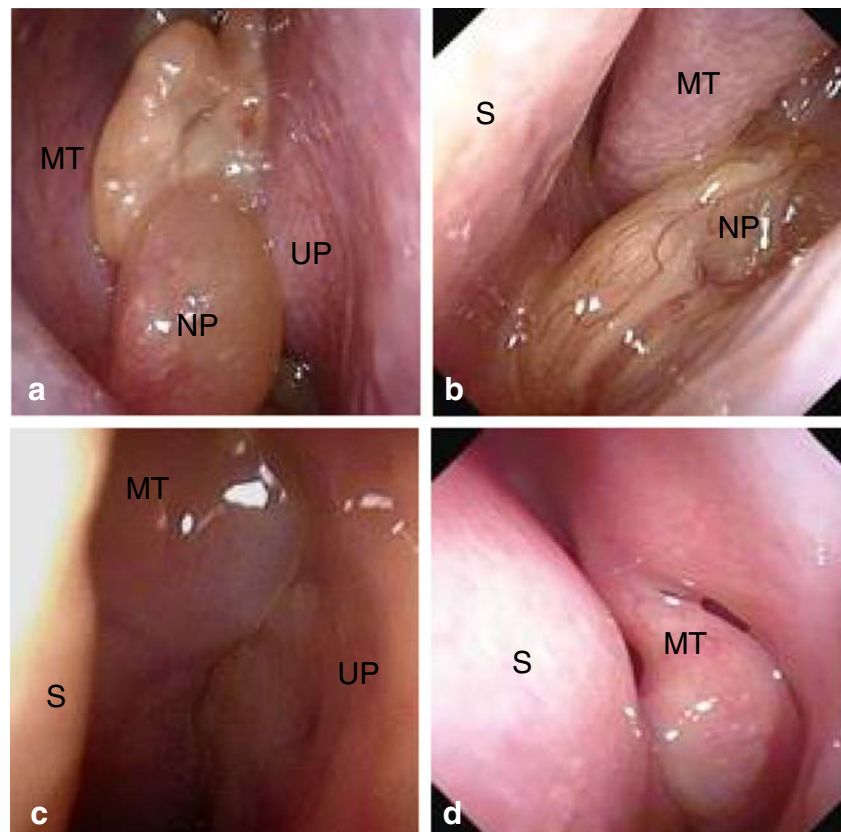
with allergy testing and management, rather than steroids or antibiotics as typically used in CRS [40]. DelGaudio et al. have also suggested a role for allergy management in CCAD patients but have also had success with surgical treatment, implying that treatment can be patient specific with multiple routes to clinical improvement [38•].

Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is a well-recognized disease entity with diagnosis criteria defined by Bent and Kuhn in 1994. Criteria include (1) type 1 hypersensitivity confirmed by history, skin tests, or serology, (2) nasal polyposis, (3) radiologic findings of seriginous areas of high attenuation in the affected sinuses (heterogenous opacification), (4) eosinophilic mucin without fungal invasion, and (5) positive fungal stain of contents removed during surgery [41•]. Given these diagnostic criteria, there is suggestion of an allergy-mediated process precipitating disease in AFRS.

Wise et al. studied patients with AFRS diagnosed per the Bent and Kuhn criteria to further characterize the involvement of type I hypersensitivity reactions. They noted that AFRS patients had systemic allergy testing showing hypersensitivity to fungal as well as non-fungal antigens. When comparing AFRS, CRSsNP, and control patients, the AFRS cohort was noted to

Fig. 1 Nasal endoscopy and imaging findings in CRSwNP vs. CCAD. Panels A and B represent nasal endoscopy findings in CRSwNP. In both images, nasal polyps obscure the middle meatus and medialize the middle turbinate. Panels C and D represent nasal endoscopy findings in CRSwNP. Both images show polypoid changes to the middle turbinate. Image D also shows polypoid changes to the septum. (MT, middle turbinate; UP, uncinate process; NP, nasal polyp; S, septum)



have significantly higher levels of IgE in sinonasal tissue, especially in the epithelial and subepithelial regions of the inferior turbinate and sinus tissue. Furthermore, they noted IgE in sinonasal tissue specific for *Cladosporium*, *Aspergillus*, Timothy grass, red maple, cockroach, ragweed, and cocklebur [42, 43]. This lends itself to the theory that AFRS is indeed allergy mediated, both systemically and locally in sinonasal tissue.

While type I hypersensitivity reactions are likely to be involved in pathogenesis of AFRS, it is unclear to what degree. Schubert et al. found that the most common fungal species isolated from an AFRS cohort in the Southwestern United States was *Bipolaris spicifera*, found in 67% of patients. However, they found that *B. spicifera*-specific IgE levels were not statistically different in the groups with and without *B. spicifera* seen on staining. Furthermore, they note high polyclonal serum IgE and intense eosinophilic lymphocytic mucosal inflammation disproportionate to the physical number of fungal organisms seen on staining and surgical pathology. This suggests that fungal hypersensitivity may not be the only etiology of AFRS [44].

Schubert et al. propose the theory that AFRS is intrinsically a hypersensitivity response to fungus but is propagated by superantigens. It has been previously noted that *Staphylococcus aureus* is commonly cultured along with fungal anaerobes in AFRS, but the disease is not responsive to anti-staphylococcal antibiotics. They suggest that staph may act as a superantigen, propagating disease in patients with genetic susceptibility to fungal hypersensitivity, and hypersensitivity reactions in general [45].

Currently, the mainstay of treatment for AFRS includes surgery and medical management of allergy, including sinus irrigation, antihistamines, and intranasal vs. systemic corticosteroids [46]. Prior studies have shown benefit from subcutaneous immunotherapy (SCIT) preoperatively with improved response to surgery, as well as improvement in quality of life scores and clinical endoscopic findings [47, 48]. Given growing interest in immunotherapy for AFRS, Melzer et al. conducted retrospective review to identify AFRS patients treated with sublingual immunotherapy (SLIT). They found that the cohort treated with SLIT had lower total serum IgE, Lund-Mackay scores, and improvement in quality of life scores [49].

Overall, there appears to be a relationship between allergy and AFRS; however, the degree of association remains unclear. Inflammation in AFRS may have multiple driving factors, and treatment with immunotherapy may be beneficial in adjunct to surgery and medical management of allergies.

Other Important Considerations

Several prior studies have shown a correlation between allergy and asthma in CRS patients, especially in CRSwNP compared

with CRSsNP [2, 9, 10, 21]. Additionally, those with CRSwNP are more likely to have comorbid asthma and report aspirin sensitivity than patients with CRSsNP [13].

Similarly, in pediatric populations, Sedaghat et al. have shown a significant association between allergic rhinitis and CRS, with allergic rhinitis being more prevalent than cystic fibrosis, immunologic disorders, and primary ciliary dyskinesia in the CRS population. Similar to adults, they note the coexistence of asthma and allergic rhinitis [50], with dust mite sensitivity found to be the most common allergen sensitization for children in the CRS population [51]. Atopic patients have been shown to develop CRS at younger ages than non-atopic patients. Regardless of age, however, there are no differences in severity scores of Lund-Mackay scores in the earlier onset patients [24, 51].

With regard to imaging, Brook et al. demonstrated that there is no relationship between allergic sensitization and Lund-Mackay scores for perennial and seasonal allergens in CRS patients. Furthermore, there was no increase in Lund-Mackay scores for imaging done during allergen season [52]. Hamizan et al. also found that there were no changes in imaging, regardless of seasonal timing or atopic status in patients with CRS [39].

Finally, CRSwNP and CRSsNP have both been implicated in the propagation of food allergy. Liu et al. initially showed that CRS patients with food allergies who underwent FESS had reductions in food allergy symptoms provoked by oral intake. They showed decreased serum levels of Th2 cytokines and food specific IgE. Furthermore, they found high concentrations of staphylococcal enterotoxin B (SEB) in sinonasal washings and stool samples of CRS patients with food allergies (CRS-FA) than CRS patients without food allergies. When cultured with SEB, CRS-FA peripheral monocytes produced increased levels of IL-4, a response that was maintained only until the removal of SEB. They suggest that FESS may lead to the attenuation of food allergies, because of the decrease in SEB being swallowed and disrupting the immune balance of the gastrointestinal tract [53]. In a later study, Yang et al. again showed higher SEB load in CRS-FA patients. They used mouse models to show that sinonasal SEB proteins were swallowed and degraded into peptides that stimulated gastrointestinal dendritic cell growth, migration, and T cell response modulation, propagating food allergy symptoms [54].

Conclusions

There is no clear association between allergic rhinitis and CRSwNP. Current literature suggests that allergy may contribute to pathogenesis of disease in CRSwNP but is likely less involved in symptom severity, imaging findings, or disease recurrence. The role of allergy in CRSsNP is even less clear, as much of the current literature delves into the relationship between allergy and CRSwNP, but relatively little has been published

regarding CRSsNP specifically. It is possible that there is a component of allergic inflammation implicated in the development of CRSsNP, but there is also likely a role for environmental exposures and irritants causing sinonasal remodeling. Both conditions, however, are almost certainly multifactorial.

CCAD is an allergy-driven process that should be treated as a distinct disease process from CRSwNP. It is characterized most commonly by middle turbinate edema and polypoid changes causing obstruction and sinus involvement in advanced disease. While it has often been considered a variant of CRSwNP, it should be considered a distinct entity and should be managed primarily with allergy testing and allergy treatment, among other possible interventions. Proper diagnosis and distinction from CRSwNP is, therefore, of the utmost importance. Further work must be done to further distinguish CRS and CCAD to better clarify the association of both with allergy and eliminate the confounding inclusion of CCAD.

AFRS likely is a multifactorial disease process with some involvement of allergy in disease propagation and development. The degree of involvement of allergy remains unclear; however, medical management of allergies and surgery remains the mainstay of management. There is a potential role for immunotherapy in disease modulation, but further work must be done to establish the benefit of these therapies and the most efficacious regimens.

Finally, it is worthwhile to further classify patients with CRS into atopic and non-atopic groups. Several studies suggest that the two have different inflammatory profiles. This becomes important when considering treatment options because the diagnosis of allergic disease allows for a wider array of treatment options, including allergen-specific immunotherapy.

Compliance with Ethical Standards

Conflict of Interest Christopher D. Brook reports personal fees from GI Reviewers and from Canon, Inc. Pratima Agarwal declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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