



The connection between seasonal allergies, food allergies, and rhinosinusitis: what is the evidence?

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Purpose of review

Rhinosinusitis affects an estimated one in seven adults in the United States. Otolaryngologists are intimately involved in the care of patients with rhinosinusitis and other upper airway inflammatory conditions through procedures such as endoscopic sinus surgery and, therefore, would benefit from a deeper understanding of the associated comorbidities and their management. Recent evidence has suggested several connections between the underlying disease of rhinosinusitis, seasonal allergies, and food allergies. The authors of the present review seek to provide a focused analysis of the recent literature with respect to epidemiology, pathophysiology, and treatment options concerning these conditions.

Recent findings

Evidence has connected the function of filaggrin, a skin barrier protein, with the pathogenesis of allergic rhinosinusitis and food allergy. Additionally, decreased levels of regulatory B cells and T cells are associated with and play a role in atopic disease. Overlapping treatment modalities between these conditions suggest similar conclusions.

Summary

Future research into the role of the skin barrier, regulatory immune cell functioning, transforming growth factor- β , and other cytokine signaling, and treatment options such as omalizumab and azelastine is likely to have profound impact on clinicians' management of patients with these disorders and their comorbidities.

Keywords

atopy, food allergies, rhinosinusitis, seasonal allergies, sinusitis

INTRODUCTION

Rhinosinusitis affects approximately one in seven adults in the United States [1]. Chronic rhinosinusitis (CRS), a subset of rhinosinusitis, accounts for over 14 million emergency room and clinic visits annually, amounting to nearly 7% of all outpatient medical visits [2]. Moreover, the economic impact of CRS is significant, with direct costs exceeding \$8.6 billion annually [3]. The cause of these conditions is often allergic (allergic rhinosinusitis) or infectious, with the current mainstays of treatment including corticosteroids, antimicrobials, antihistamines, and immunotherapy; for recalcitrant cases, sinus surgery is a beneficial option. An estimated 350 000 open and endoscopic [endoscopic sinus surgery (ESS)] sinus procedures are performed in the United States each year [4]. A recent analysis of ESS for CRS in 9105 patients with other respiratory comorbidities (asthma, polyps, aspirin sensitivity, and allergies) demonstrated that ESS significantly reduced subsequent healthcare needs and costs for all patients [5]. As new and effective treatment modalities such

as ESS continue to be researched and developed, otolaryngologists remain deeply involved in the evolving care for patients suffering from rhinosinusitis. Thus, it is vital that clinicians have an understanding of the most recent literature involved in the management not only of rhinosinusitis, but also the comorbidities associated with this condition.

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KEY POINTS

- Compromised skin barrier competence from mutations in the filaggrin protein is associated with rhinosinusitis and food allergy.
- Decreased levels of T-regulatory and B-regulatory lymphocytes are associated with allergic disease; additionally, B-regulatory levels are shown to increase with allergen-specific immunotherapy.
- Disorders of TGF- β signaling increase serum IgE levels and predispose patients to various atopic phenotypes, including eczema, rhinosinusitis, and food allergy.
- Several drugs, including omalizumab and azelastine, show promise in the treatment of more than one allergic disorder in preliminary studies.

It has been demonstrated that rhinosinusitis is associated with the development of polyposis, bronchial inflammation, and mucosal abnormalities [6]. Recent evidence also suggests that the underlying cause of rhinosinusitis shares common pathways with various additional atopic phenotypes such as food allergy and seasonal allergy. It is valuable for practitioners in multiple specialties, including otolaryngology, allergy, primary care, pulmonology, and gastroenterology, to understand the clinical, pathophysiologic, and epidemiologic similarities among these disorders to prevent and treat them more effectively. The authors of the present review seek to elucidate the seemingly nebulous connection between rhinosinusitis, food allergy, and seasonal allergy through a review of the recent literature.

EPIDEMIOLOGIC EVIDENCE

Epidemiologic evidence suggests a link between seasonal allergy, food allergy, and rhinosinusitis. However, the evidence is either weak or outdated. Even recent analyses of the role of allergy in the pathophysiology of CRS tend to cite various epidemiologic studies from decades ago (1978–2000). The general findings from these older studies demonstrated that more than 50% of patients with allergic rhinosinusitis have clinical and/or radiographic evidence of CRS; between 25% and 58% of individuals with rhinosinusitis have aeroallergen sensitization; and both multiple allergen sensitivity and perennial allergen sensitivity are independently associated with an increased likelihood of CRS [7–10]. Although these studies do in fact suggest a connection between these three disorders, there is a paucity of subsequent epidemiologic studies to further support this correlation.

The few recent epidemiologic studies that have demonstrated a connection have lacked randomization and/or comparisons with matched control groups, thus weakening their statistical power. For instance, in a recent single-institution study evaluating comorbidities in patients undergoing ESS for CRS, 38.7% of patients demonstrated inhalant allergy, but the statistical significance of this result could not be established because of the lack of a matched control group [6]. Similarly, a 2011 prospective analysis of the relationship between food allergy and rhinosinusitis demonstrated a significantly higher incidence of cow's milk allergy in patients with chronic polypoid rhinosinusitis, but the population was limited to a single institution [11]. Additionally, a retrospective study of 13 215 children in Japan aged 7–15 years found a significantly higher incidence of allergic rhinosinusitis, bronchial asthma, atopic dermatitis, and allergic conjunctivitis in children who were allergic to eggs, milk, or wheat in their infancy; however, the study was questionnaire-based and, moreover, the food allergy had resolved itself in 80% of the cases by age 4 [12]. Further investigation of the concurrent incidence of food allergies and rhinosinusitis can facilitate the clinical diagnosis and management of these disorders, in addition to elucidating a possible common genetic or environmental cause.

PATHOPHYSIOLOGIC EVIDENCE

A complex interplay between a genetic susceptibility and environmental stressors leads to the development of allergic phenotypes. These conditions are characterized by an inflammatory immune response following the introduction of a foreign immunogenic antigen and the possible development of chronic symptoms, even without the need for continuous antigenic stimulation. The most widely established and common pathway for these conditions is characterized by a TH2-type response to allergen. Following the presentation of antigen via major histocompatibility complex II on an antigen-presenting cell, CD4+ T-cells can undergo many phenotypic switches, with one of them being TH2. Although it is still relatively unknown what drives a CD4+ cell to choose the TH2 fate, current research is focusing on establishing the biochemical mechanism. TH2 cells are characterized by the set of cytokines they release, including interleukin-4, interleukin-5, interleukin-9, and interleukin-13. Interleukin-4 induces class-switching of B cells into plasma cells that secrete IgE antibody to the antigen in question. Interleukin-5 is a chemotactic factor responsible for the maturation and recruitment of eosinophils, either systemically

or locally [13]. IgE in circulation subsequently attaches to the surface of mast cells. Enough offending antigen can cross-link IgE on mast cell surfaces and subsequently trigger the release of various inflammatory mediators via mast cell degranulation. These inflammatory mediators, including histamine, platelet-activating factor, and many others, are responsible for the symphony of symptoms associated with anaphylaxis. These include vasodilation and self-perpetuation of the immune response via the recruitment of more lymphocytes and inflammatory cells [14]. In addition, these mediators contribute to the symptomatology via neuromodulatory effects on nearby sensory afferent fibers [15]. The remainder of this section will focus on new insight and future directions of research regarding the overlap in the pathophysiology underlying these conditions.

Evidence suggests that different routes of exposure can promote either sensitization or tolerance to the offending antigen [16]. With respect to this principle, it has recently been demonstrated by Linneberg *et al.* [17^{***}] through genotyping analysis and self-reporting of allergic symptoms that loss-of-function mutations of the filaggrin (FLG) gene are significantly associated with food allergy and alcohol sensitivity when compared to individuals with the wild-type FLG allele. Filaggrin is an epidermal protein that plays a vital role in preventing exposure to antigen by maintaining the barrier function of the skin, simultaneously supporting normal skin flora and protecting against ultraviolet radiation [18]. Loss-of-function mutations of this gene are significantly associated with allergic rhinosinusitis and atopic dermatitis, suggesting a common cause with food allergy [17^{***}]. Even in patients with wild-type FLG genes, TH2 cytokines have been shown to reduce the activity of FLG, thus increasing susceptibility to immunogens [19]. Further research into the skin barrier and its relationship to atopy may provide greater insight into the pathogenesis and treatment modalities.

Recent research has also been investigating the role of regulatory T cells (T-regs) and B cells (B-regs), both of which are high in nonallergic individuals, in the pathogenesis of allergic disease [20]. A recent analysis by Stelmaszczyk-Emmel *et al.* [21^{*}] found significantly fewer T-regs (as a percentage of all CD4⁺ cells) in children with atopic dermatitis and/or food allergy when compared with healthy controls, as well as a significant negative correlation between serum IgE levels and T-regs. This implies that T-reg percentage is associated with serum IgE levels, an established mediator of atopic disease. However, they also found significantly higher FoxP3 expression, a transcription factor responsible for

maturation of T-regs in the thymus and maintenance of their immunosuppressive function, in allergic individuals when compared with healthy controls. The lack of explanation for this seemingly contradictory result warrants further investigation into the role of FoxP3 in T-reg development [21^{*}]. Moreover, coculture of B-regs with T-regs enhanced T-reg properties via FoxP3 upregulation [20]. Another recent study by van de Ween *et al.* [22^{*}] demonstrated that interleukin-10-secreting B-regs (BR1 cells) induced IgG4-producing plasma cells; IgG4 is a noninflammatory antibody, and interleukin-10 is a potent immunosuppressant. They also found that allergen-specific immunotherapy (or SIT, consisting of high dose allergen exposure) for allergic patients induced proliferation of BR1 cells and increased serum IgG4 levels [22^{*}]. Both of these studies provide preliminary evidence of the immunomodulatory effects of T-regs and B-regs, as well as a connection with atopic disease.

Transforming growth factor (TGF)- β signaling has been shown to have an immunomodulatory function. A recent study by Frischmeyer-Guerreiro *et al.* [23^{*}] investigated the development and prevalence of allergic disease in patients with Loey-Dietz syndrome (LDS), a genetic disorder characterized by mutations in either TGF- β or a TGF- β receptor. Their findings suggest a complex involvement of TGF- β T-cell lineage and the development of allergic disease. They found that LDS patients are significantly more likely to develop allergic disease (including food allergy, eczema, allergic rhinosinusitis, and others) when compared with controls without LDS; additionally, LDS patients had significantly higher levels of serum IgE, eosinophils, and TH2 cytokines. *In vitro*, they found that TGF- β stimulation of naïve CD4⁺ cells caused increased proliferation of TH2-cytokine-producing cells in cells from LDS patients when compared with cells from healthy controls [23^{*}]. A study by Ma and Yin [24^{*}] comparing pollinosis sufferers with and without food allergy (and food allergy further subdivided into a systemic reaction, oral allergy, and anaphylaxis) compared with healthy controls found significantly higher TGF- β levels in sufferers of both food allergy and pollinosis, suggesting another common etiologic factor between allergic syndromes. All pollinosis sufferers had significantly lower levels of interleukin-10, but the lowest levels were associated with the most severe food allergy symptoms. The highest serum TGF- β levels were in the anaphylaxis sufferers, providing further evidence in TGF- β 's signaling role in TH2 lineage differentiation [24^{*}].

Tryptase is a serine protease contained in mast cell secretory granules and, as such, it can serve as a

marker of mast cell activation. A study by Lyons *et al.* [25[¶]] investigated the prevalence of allergic disease and symptomatology in nine families who were found to have high serum tryptase inherited in an autosomal dominant fashion (tryptasemia). A significant positive correlation between serum tryptase levels and presence of both gastrointestinal symptoms (irritable bowel syndrome, gastrointestinal reflux, and others) and atopic symptoms (environmental allergies and asthma) was observed, along with several other trends. Moreover, bone marrow biopsy in five of nine index subjects from each family showed mastocytosis without a clonal mast cell disorder [25[¶]]. Further analysis of patients with a constellation of symptoms similar to those seen in this study could very well lead to discovery of inheritable allergic syndromes of immune system dysfunction, similar to that seen in LDS.

TREATMENT EVIDENCE

The pathophysiologic overlap among these three conditions makes them amenable to similar treatment regimens. Although systemic and/or topical corticosteroids and antihistamines are established and well known treatments for these disorders, newer drugs with more targeted mechanisms of action have also been demonstrated to be effective. Because of the immune hyperreactivity that underlies the pathogenesis of these conditions, it is logical that immunosuppression by corticosteroids may provide relief; however, more targeted therapy instead of overall immunosuppression may lead to better patient outcomes without the side-effects of corticosteroid treatment.

The most promising of these drugs is omalizumab, a monoclonal antibody against IgE. Tsabouri *et al.* [26^{¶¶}] recently carried out a systematic review of 11 randomized controlled trials with 2870 patients, which demonstrated that omalizumab significantly improved symptoms of both seasonal and perennial allergic rhinosinusitis and decreased rescue medication use, but had no impact on the incidence of adverse effects. In addition to seasonal and perennial allergies, anti-IgE drugs have also shown promise in treating food allergy since 2003, when Leung *et al.* [27] examined the effects of TNX-901, an anti-IgE molecule, in a randomized, double-blind, placebo-controlled study. The study demonstrated significantly increased end-study peanut tolerance in the allergic group, which received high doses of TNX-901, but there was no difference in adverse event incidence when compared with placebo. Unfortunately, subsequent studies with omalizumab and other IgE drugs have been

precluded by various obstacles. For example, a phase II trial in 2011 was terminated early because two subjects experienced severe anaphylactic reactions at study entry [28]. The limited data from the 14 subjects who completed the study did demonstrate increased peanut tolerance when compared with placebo, but the difference was not statistically significant. The strongest evidence comes from a separate nonplacebo-controlled trial carried out by Savage *et al.* [29] in 2012, which demonstrated an approximately 80-fold increase in peanut tolerance (80–6500 mg) over 6 months. This study, however, was limited by its small sample size ($n=14$). At present, Bégin *et al.* [30] have prepared a phase I single-site protocol investigating the safety and tolerability of oral immunotherapy using omalizumab to desensitize individuals to multiple foods simultaneously.

Another drug that was recently investigated by Luo *et al.* [31] is azelastine, a second-generation antihistamine that can potentiate antiallergenic effects of corticosteroid treatment. It was found that combining azelastine with budesonide (a corticosteroid) *in vitro* was able to upregulate expression of mitogen-activated protein kinase phosphatase-1 (MKP-1), an anti-inflammatory gene induced by corticosteroids, more than with budesonide alone. MKP-1 expression decreases intercellular adhesion molecule-1 (ICAM-1) expression, a molecule required for the extravasation of inflammatory cells from the bloodstream. Additionally, the administration of budesonide and azelastine together significantly decreased ICAM-1 expression and total nasal symptom score when compared to budesonide therapy alone when administered for 2 weeks to six patients with severe allergic rhinosinusitis [31]. Because ICAM-1 plays an important role in allergic phenotypes, further research into azelastine, not only for the treatment of rhinosinusitis, but also for food allergy, should be considered.

As discussed earlier, TGF- β gene mutations are also strongly associated with a predisposition to allergy and, therefore, certain drugs that modulate TGF- β signaling may prove effective in treating allergy and atopy. One drug that holds promise in this regard is losartan, an angiotensin-II inhibitor, which has been demonstrated to antagonize the TGF- β signaling cascade through an unknown mechanism [23[¶],32]; however, its effectiveness against allergy has not yet been investigated.

CONCLUSION

This review has summarized the evidence of connections underlying the disease of rhinosinusitis,

seasonal allergies, and food allergies through an analysis of the most recent literature on the epidemiology, pathophysiology, and treatment of these conditions. It has already been established that an overactive immune response characterized by TH2 helper T cells underlies these conditions, and new evidence regarding the roles of filaggrin, B-regs and T-regs, TGF- β , and other cytokines suggest a common pathogenesis. Overlapping treatment modalities suggest similar conclusions. Further investigation into these connections is vital to strengthen our understanding of the disease processes and to influence clinical decision-making when physicians are confronted with the millions of patients who suffer from these disorders.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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