Determining the role of allergy in sinonasal disease

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ABSTRACT

The contributing role of specific IgE sensitization in the pathophysiology of sinonasal diseases including rhinitis, chronic rhinosinusitis (CRS), and nasal polyps is explored. Although it is estimated that sensitization to environmental allergens is present in 75% of patients with rhinitis, the role of allergy in CRS and nasal polyps is less certain. However, when atopy is present in the setting of nasal polyps, it is associated with worse quality of life and a higher incidence of asthma. Several theories have been put forth whereby inhalant aeroallergen exposure could drive the inflammatory response that occurs both in the nose and in the sinuses. Tools available to determine the presence of allergic sensitization include skin tests for immediate hypersensitivity, in vitro testing for allergen-specific IgE, and nasal allergen provocation testing. Whether by skin testing or in vitro testing, the identification of specific IgE requires clinical correlation with the history and physical exam.

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Specific IgE sensitization plays a major contributory role in the pathophysiology of upper and lower respiratory diseases including rhinitis and asthma. Although it is estimated that allergic sensitization to environmental allergens is present in 75% of patients with rhinitis,¹ the role of allergy in chronic rhinosinusitis (CRS) and nasal polyps is less certain.² In this article the role of allergy in sinonasal disease is explored, followed by an overview of diagnostic testing tools for determining immediate hypersensitivity.

EPIDEMIOLOGY OF ALLERGIC RHINITIS IN CRS

There exists a high degree of overlap between CRS³ and allergic rhinitis,⁴ but this relationship may be more coincidental than etiologic.⁵ Eighty-two percent of patients in an academic institution who underwent sinus surgery were noted to have one or more positive skin-prick test results to inhalant allergens. This was significantly higher than that found in the National Health and Nutrition Examination Study III (54.3%) but comparable with the rhinitis control group (72%) that did not have CRS.⁶ Although IgE-mediated hypersensitivity occurs in patients with CRS, the weight of the available evidence suggests that allergic rhinitis contributes in a variable but limited way to the mucosal inflammation of CRS.² For example, in a retrospective study of pediatric patients, allergy was shown to be a risk factor for protracted symptoms despite endoscopic sinus surgery; however, there is no evidence to support the theory that failure to address allergy adversely affects the probability of success in sinus surgery.⁷

With regard to nasal polyps, the prevalence in a population with allergic rhinitis is comparable with that seen in the normal population⁸; and allergy does not appear to be a risk factor for the development of nasal polyps.^{9,10} Additionally, the presence of allergy does

not correlate with polyp size, symptom scores, grading of severity by CT (Lund-Mackay), or rate of polyp recurrence.¹¹ However, the presence of atopy in the setting of nasal polyps has been shown to be associated with lower quality of life scores and a higher incidence of asthma.¹² Furthermore, there appears to be some subsets of CRS where IgE sensitization may play a greater role. Among these are patients with severe CRS with nasal polyps (CRSwNPs)¹³ who often manifest chronic hyperplastic eosinophilic sinusitis in association with multiple positive skin tests,⁵ allergic fungal rhinosinusitis,¹⁴ and patients with local polyclonal IgE in the absence of systemic atopy, the potential etiology of which is discussed in this article.¹⁵

THEORIES FOR ALLERGIC RHINITIS/CRS PATHOPHYSIOLOGICAL LINKAGE

Discussion is warranted regarding several theories whereby inhalant aeroallergen exposure could drive the inflammatory response when it occurs concomitantly in the nose and sinuses (Table 1).⁵ A “direct aeroallergen reaction” is thought to be unlikely because breathing alone does not drive aeroallergens into the sinuses of patients who have not had their sinus ostia altered by surgery.⁵ Except for the CRS subtype known as allergic fungal rhinosinusitis,¹⁴ evidence for “sensitization to colonizing fungi” in the pathogenesis of CRS appears to be limited to playing a role as a disease modifier.² There exists greater supporting evidence for a “systemic allergic inflammatory process” involving the local nasal airway, nasal-associated lymphatic tissue, the bone marrow, and the sinuses. Supporting this concept, nasal allergen challenge has been shown to result in inflammatory changes within both the ipsilateral, but strikingly, also the contralateral maxillary sinus cavity, marked by a significant increase in maxillary sinus eosinophils.¹⁶ Finally, the “sensitization to colonizing bacteria” hypothesis proposes that in CRSwNPs, exposure to *Staphylococcus aureus* enterotoxins, induces an inflammatory mucosal response, resulting in a skewing of T lymphocytes toward a Th2 phenotype, proinflammatory cytokine release, localized polyclonal IgE responses, Treg inhibition, and accentuated eosinophil and mast cell activity.^{17–19} Superantigen-induced polyclonal IgE in airway disease has been postulated to contribute to chronic inflammation by continuously activating mast cells. In studies where tissue fragments from nasal polyp patients were stimulated with anti-IgE, mast cells were activated, indicating that mucosal IgE antibodies in nasal polyp tissue are functional and able to activate mast cells.²⁰ The polyclonal IgE response may be directed at bystander pathogens

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Table 1 Putative mechanisms linking allergic rhinitis to CRS

Direct aeroallergen reaction
Sensitization to colonizing fungi
Systemic allergic inflammation
Sensitization to colonizing bacteria

Source: Adapted from Ref. 5.
CRS = chronic rhinosinusitis.

such as the *Staphylococcus* enterotoxin. The role of IgE sensitization to bystander pathogens is supported by anti-IgE clinical trial outcomes showing improvement in nasal polyps irrespective of the presence of allergic sensitization to aeroallergens.^{21,22}

DIAGNOSTIC TESTING FOR IMMEDIATE HYPERSENSITIVITY

Despite uncertainties regarding the contribution of allergy to CRS, knowledge of specific allergic sensitizations may provide benefit to patients who suffer from associated rhinitis symptoms. The primary tools available to determine the presence of IgE-mediated hypersensitivity²³ include skin tests and *in vitro* tests for allergen-specific IgE. Although both techniques are able to identify specific IgE-mediated hypersensitivity, skin testing by prick/puncture technique is the preferred diagnostic approach because of its overall sensitivity, specificity, and rapidity of performance.^{24–28} Skin testing detects the presence of allergen-specific IgE bound to mast cells by eliciting allergen-induced mast cell degranulation and a resultant histamine wheal/flare response. For a detailed description of the skin test procedure, the reader is referred to diagnostic testing practice parameters.²⁴

Factors that may affect interpretation and reliability of prick/puncture tests include the skill of the tester, the test instruments, extremes of age, skin color, skin reactivity (including dermatographism), and reagent potency. Additionally, concurrent medications affect the validity of skin testing; in particular, first-/second-generation antihistamines and tricyclic antidepressants should be held for 3–7 days depending on the agent, and H₂-antagonists for 1 day.²⁴ Although β -adrenergic blocking agents do not interfere with the skin test response, caution with their concomitant use is warranted because of the potential of β -blockers to impede epinephrine treatment of anaphylaxis, which is a rare but potential adverse reaction of skin testing.²⁹ Because of this risk, a physician should always be available to administer emergency epinephrine if necessary.^{30–32}

Ideally, objective wheal-and-flare responses are recorded in millimeters, along with positive and negative controls. In the clinical setting of strongly suspected hypersensitivity, intracutaneous tests (at 100- to 1000-fold more dilute) may be applied if prick/puncture tests are negative. Intracutaneous tests are associated with increased risk of inducing anaphylaxis, which can be fatal.³³ This is more of a safety concern when/if intracutaneous tests are performed without preceding prick/puncture tests. Interpretation of intracutaneous tests may be confounded by false positive results because of irritant effects of the testing reagent.

Immunoassays measuring serum-specific IgE concentrations (kIU/L) have good sensitivity/specificity and can predict respiratory responses after allergen exposure.^{24,28} These assays provide information that is not equivalent to skin testing but is considered complementary.³⁴ The clinical efficacy of a total IgE measurement is limited; it is much more valuable to measure serum-specific IgE. There are circumstances when serum-specific IgE immunoassays may be preferable to skin testing such as in the setting of generalized dermatitis, concomitant medications that may suppress the skin test, uncooperative patients, or when the history suggests an unusually greater risk of anaphylaxis from skin testing.²⁴

Whether by skin testing or *in vitro* testing, the identification of specific IgE requires clinical correlation with the history and physical exam.²⁴ In circumstances where the history strongly suggests allergen sensitivity, but testing for specific IgE is negative, a nasal allergen provocation test and/or detection of local nasal specific IgE may confirm the diagnosis.³⁵ In this condition, referred to as “entropy,” local IgE production may be limited to the nasal mucosa in patients who would otherwise be diagnosed as having nonallergic rhinitis.^{36,37}

Finally, despite advances in evidence-based medicine, unproven tests continue to be promoted for the determination of allergic sensitization. These include IgG4-specific antibody tests, cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, and hair analysis.³⁸ Currently, there is neither evidence nor an immune/mechanistic basis to suggest that these tests are useful.

SUMMARY

Specific IgE sensitization plays a contributing role in sinonasal disease, particularly in rhinitis, but also to an undetermined and variable extent in CRS and nasal polyps. Although it is estimated that allergic sensitization to environmental allergens is present in 75% of patients with rhinitis, the role of allergic contribution to CRS is less certain. However, when atopy is present in the setting of nasal polyps, it is associated with worse quality of life and a higher incidence of asthma. Several theories have been put forth whereby inhalant aeroallergen exposure could drive the inflammatory response that occurs both in the nose and sinuses. In patients with CRS or nasal polyps, when the history suggests the presence of allergic sensitization, skin testing is the preferred test for the determination of immediate hypersensitivity. In certain clinical settings, *in vitro* testing for allergen-specific IgE provides an additional diagnostic tool. Finally, a nasal allergen provocation test may confirm the presence of local allergy in the setting of negative skin tests, but its efficacy is limited because of labor intensity and because it is confounded by the potential for false positive results. Whether by skin testing or *in vitro* testing, the identification of specific IgE sensitization, when clinically correlated with the history and physical exam, allows the clinician to best determine and treat the allergic contribution to sinonasal disease. Once an allergic contribution has been determined, the clinician must weigh the medical evidence as to what therapeutic interventions, including immunotherapy,³⁹ are appropriate.

CLINICAL PEARLS

- Although specific IgE sensitization can be determined by *in vitro* assay, prick/puncture skin test technique provides more rapid results, which, unlike *in vitro* tests, are not influenced by high total IgE levels.
- Interpretation of skin testing may be confounded by extremes of age, skin color, dermatographism, and antihistamine use.
- Interpretation of skin testing should be performed by an experienced practitioner, in the presence of positive and negative controls.
- Because skin testing may potentially result in anaphylaxis, a physician should always be available to administer epinephrine if necessary.
- Whether by skin testing or *in vitro* testing, the identification of specific IgE requires clinical correlation with the history and physical exam to make the diagnosis of allergy.
- In a condition known as entropy, specific IgE sensitization can only be identified in the nasal mucosa and can not be found systemically.

REFERENCES

1. Settipane RA. Rhinitis: A dose of epidemiological reality. *Allergy Asthma Proc* 24:147–154, 2003.
2. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl* 23:1–298, 2012.

3. Settipane RA, Peters AT, and Chandra R. Chronic rhinosinusitis. *Am J Rhinol Allergy* 27:S11–S15, 2013.
4. Settipane RA, and Schwindt C. Allergic rhinitis. *Am J Rhinol Allergy* 27:S52–S55, 2013.
5. Kennedy JL, and Borish L. Chronic sinusitis pathophysiology: The role of allergy. *Am J Rhinol Allergy* DOI: 10.2500/ajra.2013.27.3906 [Epub ahead of print date April 18, 2013].
6. Tan BK, Zirkle W, Chandra RK, et al. Atopic profile of patients failing medical therapy for chronic rhinosinusitis. *Int Forum Allergy Rhinol* 1:88–94, 2011.
7. Lee TJ, Liang CW, Chang PH, and Huang CC. Risk factors for protracted sinusitis in pediatrics after endoscopic sinus surgery. *Auris Nasus Larynx* 36:655–660, 2009.
8. Kern R. Allergy: A constant factor in the etiology of so-called mucous nasal polyps. *J Allergy* 4:483, 1993.
9. Erbek SS, Erbek S, Topal O, et al. The role of allergy in the severity of nasal polyposis. *Am J Rhinol*. 2007 21:686–690, 2007.
10. Settipane GA. Epidemiology of nasal polyps. In *Nasal Polyps: Epidemiology, Pathogenesis and Treatment*. Settipane GA, Lund VJ, Bernstein JM, and Tos M (Eds). Providence, RI: OceanSide Publications, 17–24, 1997.
11. Pearlman AN, Chandra RK, Chang D, et al. Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy. *Am J Rhinol Allergy* 23:145–148, 2009.
12. Dávila I, Rondón C, Navarro A, et al. Aeroallergen sensitization influences quality of life and comorbidities in patients with nasal polyposis. *Am J Rhinol Allergy* 26:e126–e131, 2012.
13. Settipane RA, Peters AT, and Chiu AG. Nasal polyps. *Am J Rhinol Allergy* 27:S20–S25, 2013.
14. Laury AM, and Wise SK. Allergic fungal rhinosinusitis. *Am J Rhinol Allergy* 27:S26–S27, 2013.
15. Bachert C, Gevaert P, Holtappels G, et al. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol* 107:607–614, 2001.
16. Baroody FM, Mucha SM, Detineo M, et al. Nasal challenge with allergen leads to maxillary sinus inflammation. *J Allergy Clin Immunol* 121:1126–1132.e7, 2008.
17. Van Crombruggen K, Zhang N, Gevaert P, et al. Pathogenesis of chronic rhinosinusitis: Inflammation. *J Allergy Clin Immunol* 128: 728–732, 2011.
18. Kim DW, Khalmuratova R, Hur DG, et al. *Staphylococcus aureus* enterotoxin B contributes to induction of nasal polypoid lesions in an allergic rhinosinusitis murine model. *Am J Rhinol Allergy* 25:e255–e261, 2011.
19. Kim ST, Chung SW, Jung JH, et al. Association of T cells and eosinophils with *Staphylococcus aureus* exotoxin A and toxic shock syndrome toxin 1 in nasal polyps. *Am J Rhinol Allergy* 25:19–24, 2011.
20. Zhang N, Holtappels G, Gevaert P, et al. Mucosal tissue polyclonal IgE is functional in response to allergen and SEB. *Allergy* 66:141–148, 2011.
21. Pinto JM, Mehta N, DiTineo M, et al. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. *Rhinology* 48:318–324, 2010.
22. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol* 131:110–116.e1, 2013.
23. Uzzaman A, and Cho SH. Classification of hypersensitivity reactions. *Allergy Asthma Proc* 33(suppl 1):S96–S99, 2012.
24. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: An updated practice parameter. *Ann Allergy Asthma Immunol* 100 (suppl 3):S1–S148, 2008.
25. Tripathi A, and Kim JS. Diagnosis of immediate hypersensitivity. In *Patterson's Allergic Diseases*, 7th ed. Grammer LC, and Greenberger PA (Eds). Philadelphia, PA: J.B. Lippincott, Williams & Wilkins, 123–135, 2009.
26. Tripathi A, and Patterson R. Clinical interpretations of skin test results. *Immunol Allergy Clin North Am* 21:291–300, 2001.
27. Carr TF, and Saltoun CA. Skin testing in allergy. *Allergy Asthma Proc* 33(suppl 1):S6–S8, 2012.
28. Makhija M, and O'Gorman MRG. Common in vitro tests for allergy and immunology. *Allergy Asthma Proc* 33(suppl 1):S108–S111, 2012.
29. Greenberger PA, and Ditto AM. Anaphylaxis. *Allergy Asthma Proc* 33:S80–S83, 2012.
30. Lieberman P. The risk and management of anaphylaxis in the setting of immunotherapy. *Am J Rhinol Allergy* 26:469–474, 2012.
31. Phillips JF, Lockey RF, Fox RW, et al. Systemic reactions to subcutaneous allergen immunotherapy and the response to epinephrine. *Allergy Asthma Proc* 32:288–294, 2011.
32. Wallace DV. Anaphylaxis in the allergist's office: Preparing your office and staff for medical emergencies. *Allergy Asthma Proc* 34: 120–131, 2013.
33. Bernstein DI, Wanner M, Borish L, et al. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990–2001. *J Allergy Clin Immunol* 113:1129–1136, 2004.
34. Calabria CW, Dietrich J, and Hagan L. Comparison of serum-specific IgE (ImmunoCAP) and skin-prick test results for 53 inhalant allergens in patients with chronic rhinitis. *Allergy Asthma Proc* 30:386–396, 2009.
35. Rondón C, Campo P, Togias A, et al. Local allergic rhinitis: Concept, pathophysiology, and management. *J Allergy Clin Immunol* 129: 1460–1467, 2012.
36. Khan DA. Allergic rhinitis with negative skin tests: Does it exist? *Allergy Asthma Proc* 30:465–469, 2009.
37. Settipane RA, and Kaliner MA. Nonallergic rhinitis. *Am J Rhinol Allergy* 27:S48–S51, 2013.
38. Shah R, and Greenberger PA. Unproved and controversial methods and theories in allergy-immunology. *Allergy Asthma Proc* 33(suppl 1):S100–S102, 2012.
39. Settipane RA, Peters AT, and Borish L. Immunomodulation of allergic sinonasal disease. *Am J Rhinol Allergy* 27:S59–S62, 2013. □