

Local Allergen-Specific IgE Production in Turbinate Tissue of Pediatric Patients

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Alessandra Bliss, BS¹ , Cameron Sheehan, MD¹,
Elizabeth Erwin, MD², Kris Jatana, MD^{1,3},
and Charles A. Elmaraghy, MD^{1,3} 

Abstract

Objectives: The objective of this study is to compare serum allergen-specific IgE to IgE levels in nasal tissue taken from the inferior turbinates of pediatric patients undergoing turbinate reduction.

Methods: Twenty-six pediatric patients were recruited at the time of turbinate reduction surgery. At the time of recruitment, parents of patients completed the validated 22 item Sinonasal Outcome Test (SNOT-22) to describe symptoms prior to surgery. A sample of turbinate tissue was taken during turbinate reduction and blood was collected. Tissue and serum IgE were measured and differences in the group characteristics were evaluated using Chi-square tests for binary variables and Wilcoxon-Mann-Whitney tests for continuous variables. Student's *t* test was used to assess differences in means of total SNOT-22 scoring between the groups, and Wilcoxon-Mann-Whitney tests were used again for the rest of the SNOT-22 analysis.

Results: Levels of IgE in the serum were compared to levels in the turbinate tissue from all patients for each individual allergen. Every allergen except *Alternaria* displayed significant correlation between the serum and turbinate IgE levels. Additionally, each allergen except *Alternaria* and oak tree resulted in a strong correlation ($r > .7$) based on the correlation coefficients. Levels of *Alternaria* were found to be poorly correlative between serum and turbinate tissue, and significance was not achieved ($r = -.346$, $P = .11$).

Conclusion: Certain allergen-specific IgE antibodies in the nasal mucosa seem to be highly associated with those in the serum, based upon the significant correlations we found between the two.

Keywords

local allergic rhinitis, turbinate, pediatrics, immunoglobulin E

Introduction

Allergic rhinitis (AR) is a common disorder that affects an estimated 20% of adults and up to 40% of children.¹ AR is a category of chronic rhinitis that is associated with positive skin prick test (SPT) and serum specific IgE. In contrast, non-allergic rhinitis (NAR) has a negative SPT, negative serum specific IgE, negative nasal allergen provocation testing (NAPT), negative nasal specific IgE, and a negative basophil activation test.² AR is associated with impaired quality of life and multiple healthcare visits for appropriate diagnosis and treatment. Diagnosis is based on a clinical history of allergic symptoms including watery rhinorrhea, nasal obstruction, nasal itching, and sneezing; in addition to positive laboratory testing with skin-prick or allergen-specific immunoglobulin E (IgE) in the serum.³

Some cases of AR can be further characterized as localized AR (LAR). The term LAR was suggested by Rondón et al as a local allergic IgE production in the nasal mucosa in patients who have negative skin-prick or serum IgE

testing, thus lacking systemic atopy.^{4,5} Patients with LAR present with the nasal symptoms of AR with positive nasal allergen provocation test (NAPT) and good response to allergen specific immunotherapy; yet negative skin prick and undetectable serum IgE.⁶ Investigators have explored local IgE production in non-allergic and allergic rhinitis patients through the use of nasal lavage,^{5,7-10} surgical biopsy,¹¹ and mucosal brush biopsy.¹² Additionally, local IgE testing has expanded to investigate other upper and

¹Department of Otolaryngology-Head and Neck Surgery, The Ohio State University, Wexner Medical Center, Columbus, OH, USA

²Department of Pediatrics, Division of Allergy and Immunology, Nationwide Children's Hospital, Columbus, OH, USA

³Department of Pediatric Otolaryngology-Head and Neck Surgery, Nationwide Children's Hospital, Columbus, OH, USA

Corresponding Author:

Charles A Elmaraghy, MD, The Ohio State University, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA.
Email: Charles.elmaraghy@nationwidechildrens.org

lower airway diseases, such as nasal polyposis, asthma,¹³ and conjunctivitis.¹⁴

To date, studies have investigated quantities of local allergen-specific IgE in adult nasal mucosal tissues and compared them to IgE levels in the serum of patients with allergic symptoms.^{5,8,15} A study by Rondón et al found that LAR may start in childhood and worsen over the years.¹⁶ Further research is required to investigate the prevalence of LAR in children in comparison to children with NAR. The objective of our study was to compare serum allergen-specific IgE to IgE levels in nasal tissue taken from the inferior turbinates of pediatric patients undergoing turbinate reduction.

Methods

Subjects

Twenty-six pediatric patients were recruited at the time of turbinate reduction surgery. At the time of recruitment, parents of patients completed the validated 22 item Sinonasal Outcome Test (SNOT-22) to describe symptoms prior to surgery. The SNOT-22 provides an assessment of rhinitis-specific health status as well as quality of life that results from physical symptoms, functional limitations and emotional effects. Responses are graded using a Likert scale of severity ranging from 0 to 5, with 5 being the most severe.¹⁸ Questions range from assessing nasal issues, facial issues, sleep issues and social/emotional issues.

Serum IgE Testing

At the time of surgery, 4 mL of blood was collected from each patient. By using the ImmunoCAP 2500 (Thermo Fisher Scientific/Phadia, Uppsala, Sweden) IgE was measured to a panel of 17 allergens. Allergens tested included cat dander, dog dander, dust mites *Dermatophagoides pteronyssinus* and *farinae*, cockroach, *Alternaria*, *Cladosporium*, *Aspergillus*, elm tree, oak tree, pecan tree, walnut tree, june grass, johnson grass, bermuda grass, and ragweed.

Surgical Procedure

A sample of inferior turbinate tissue was shaved and collected from each patient during turbinate reduction surgery. Samples placed on ice were suspended in 1 mL 0.9% NaCl solution and then homogenized at 1000 rpm for 5 minutes. After homogenization, specimens were centrifuged at 3000 rpm for 10 minutes at 4°C. Supernatants were removed and tissue homogenates were stored at -80°C until testing. Samples were then analyzed for IgE levels to 12 different allergens including: cat dander, dog dander, dust mites *Dermatophagoides pteronyssinus* and *farinae*, *Alternaria*, *Aspergillus*, *Cladosporium*, Bermuda

grass, timothy grass, birch tree, oak tree, and ragweed. Values were expressed as kU/L.

Statistical Analysis

Differences in the group characteristics were evaluated using Chi-square tests for binary variables and Wilcoxon-Mann-Whitney tests for continuous. Student's *t* test was used to assess differences in means of total SNOT-22 scoring between the groups, and Wilcoxon-Mann-Whitney tests were used again for the rest of the SNOT-22 analysis. Identical tests were conducted to assess differences in the allergic rhinitis and non-allergic rhinitis groups. Correlation coefficients were determined between the turbinate tissue IgE levels and serum IgE levels for each individual allergen. Statistical analyses were performed with the assistance of online statistical software, and statistical significance was defined as $P < .05$.

Results

Patient Characteristics

A total of 26 pediatric patients were initially recruited, but 2 patients for whom specimens were not obtained were excluded. Patient age at recruitment ranged from 2 to 15 (median 9), with 29% of patients being female. A history of asthma was present in 13 patients (54%) and food allergy in 2 patients (8%). Serum analysis revealed IgE antibodies (≥ 0.35 kU/L) to at least one allergen in 10/24 (42%) patients. These patients were diagnosed with allergic rhinitis (AR) based on having allergen specific IgE in their serum, and the remaining 14 patients with IgE levels < 0.35 kU/L were considered to have non-allergic rhinitis (NAR).

Allergic Rhinitis Versus Non-allergic Rhinitis

General characteristics comparing AR patients to NAR patients are found in Supplemental Table 1. Patient age, gender, history of asthma, and food allergies were not statistically different between the 2 groups. Average bother score (patient reported measurement of symptom severity prior to surgery; Likert scale of 1-5 with 1 being not bothersome at all and 5 being as severe as it can be) was 3.6 in the AR group and 2.8 in the NAR group, although this difference was not statistically significant. Mean serum total IgE levels in the AR group (93[11-639]) were found to be statistically higher than levels in the NAR (13[1-231]) ($P = .009$).

Sinonasal Outcome Test (SNOT-22)

At the time of recruitment parents completed the 22 item Sinonasal Outcome Test (SNOT-22) to quantify

symptoms prior to surgery. Patients' SNOT-22 scores are outlined in Supplemental Table 2. Mean total score among all patients was 34.1, and the mean for the AR group was 39.7 versus 30.1 for the NAR group. Subgroup scores for the nasal domain questions were significantly different, with AR patients scoring an average of 16.4 and NAR patients averaging 9.6 ($P = .045$). The remaining subgroup scores were not found to be significantly different between the 2 groups.

Turbinate Tissue IgE Levels

Levels of allergen-specific IgE levels in the serum and the turbinate tissue for each patient are shown in Supplemental Table 3. IgE levels for allergens that were not tested in both the serum and turbinate tissue, such as elm tree and June grass (serum only), are not shown. AR patients averaged 5.9 positive serum allergens per patient, with both dust mite species, *D. pteronyssinus* (4/10 AR patients) and *D. farina* (5/10), being the most common. When assigning a cut-off of 0.35 kU/L to the turbinate tissue data, only 5 patients yielded a positive value. All 5 patients were from the AR group. The average number of positive allergens in turbinate tissue from the AR group was 2.2. The most frequent positive allergen in the local tissue was *D. pteronyssinus* (3/10 AR patients) and *Alternaria* (3/10). There were 2 additional groups of patients noted by further examination of turbinate IgE results. In the NAR group, 4 patients had detectable levels to multiple allergens from their turbinate tissue, although these values were below the cutoff (0.1–0.35 kU/L). Two of these patients (Patient 17 and 24) also had detectable levels of allergen-specific IgE in their serum, yet these were below the 0.35 kU/L cutoff. The remaining 2 patients (Patient 20 and 23) had no detectable IgE levels in their serum.

Correlation Graphs

Levels of IgE in the serum were compared to levels in the turbinate tissue from all patients for each individual allergen (Figure 1). A best-fit line correlating serum to turbinate IgE levels is present in each graph. Every allergen except *Alternaria* displayed significant correlation between the serum and turbinate IgE levels. Additionally, each allergen except *Alternaria* and oak tree resulted in a strong correlation ($r > .7$) based on the correlation coefficients. Levels of *Alternaria* were found to be poorly correlative between serum and turbinate tissue, and significance was not achieved ($r = -.346$, $P = .11$).

Discussion

This study represents an evaluation of local antigen-specific IgE production in nasal mucosal tissue of pediatric patients

with both AR and NAR. Few studies have used actual tissue surgically removed from the nasal mucosa itself when researching this topic.^{11,15,17,18} We set out to not only compare levels of allergen-specific IgE levels in the serum to levels in local nasal tissue, but also to compare local IgE production between patients with systemic atopy to those without.

We did not find clear evidence of local allergic response in patients with negative serum testing.^{3,7–10} The only patients to display IgE levels in their turbinate tissue above the cut-off value of 0.35 kU/L were those with identified systemic atopy on serum testing. This value is generally accepted in similar studies to define the lower limit of IgE in serum and local tissue and thus was used for the current study.^{16,19} Alternatively, we did find 4 patients with low levels of local IgE (<0.35 kU/L) to multiple allergens yet with negative serum testing. Despite not reaching the established cutoff, these patients may still represent a local allergy group, yet no definitive evidence can be inferred based on this data. Since this study involved only pediatric patients, it would be interesting to know if immune responses evolve as they age. A 10 years longitudinal study of adults by Rondón et al suggests that local allergic rhinitis is a separate disease process which worsens clinically over time, yet does not evolve into systemic AR.¹⁶

Our study differs from many local allergy rhinitis investigations in that no patients were challenged to antigens prior to tissue sampling, and patients underwent surgery without specific consideration to allergen seasons. A study from 2007 reported a positive response to nasal allergen provocation test (NAPT) to *D. pteronyssinus* in 54% of patients with rhinitis symptoms and negative skin testing, in addition to 22% of them demonstrating antigen-specific local IgE following NAPT.⁸ The following year, another investigation detected nasal IgE in 63% of idiopathic rhinitis patients following NAPT to grass and olive pollen.⁷ Since then, 2 additional studies have utilized NAPT in a similar manner to demonstrate nasal IgE production in NAR patients.^{5,19} Although the lack of antigen exposure before IgE testing may have contributed to the disparity of this study's results with others, certain investigators still identified baseline levels of local allergen-specific IgE without nasal provocation first. Rondón et al observed 12% of their NAR patients in one study (and 22% in another) to contain IgE antibodies in their nasal fluid prior to NAPT.^{7,8} Furthermore, Powe et al utilized tissue from nasal mucosa with no antigen challenge beforehand, yet detected local IgE production by immunohistochemistry staining in 3/10 patients with NAR.²⁰

We were also able to compare serum IgE levels to turbinate IgE levels in our patients with AR and NAR. We found that levels of IgE to every antigen except *Alternaria* correlated significantly between the serum and nasal tissue of

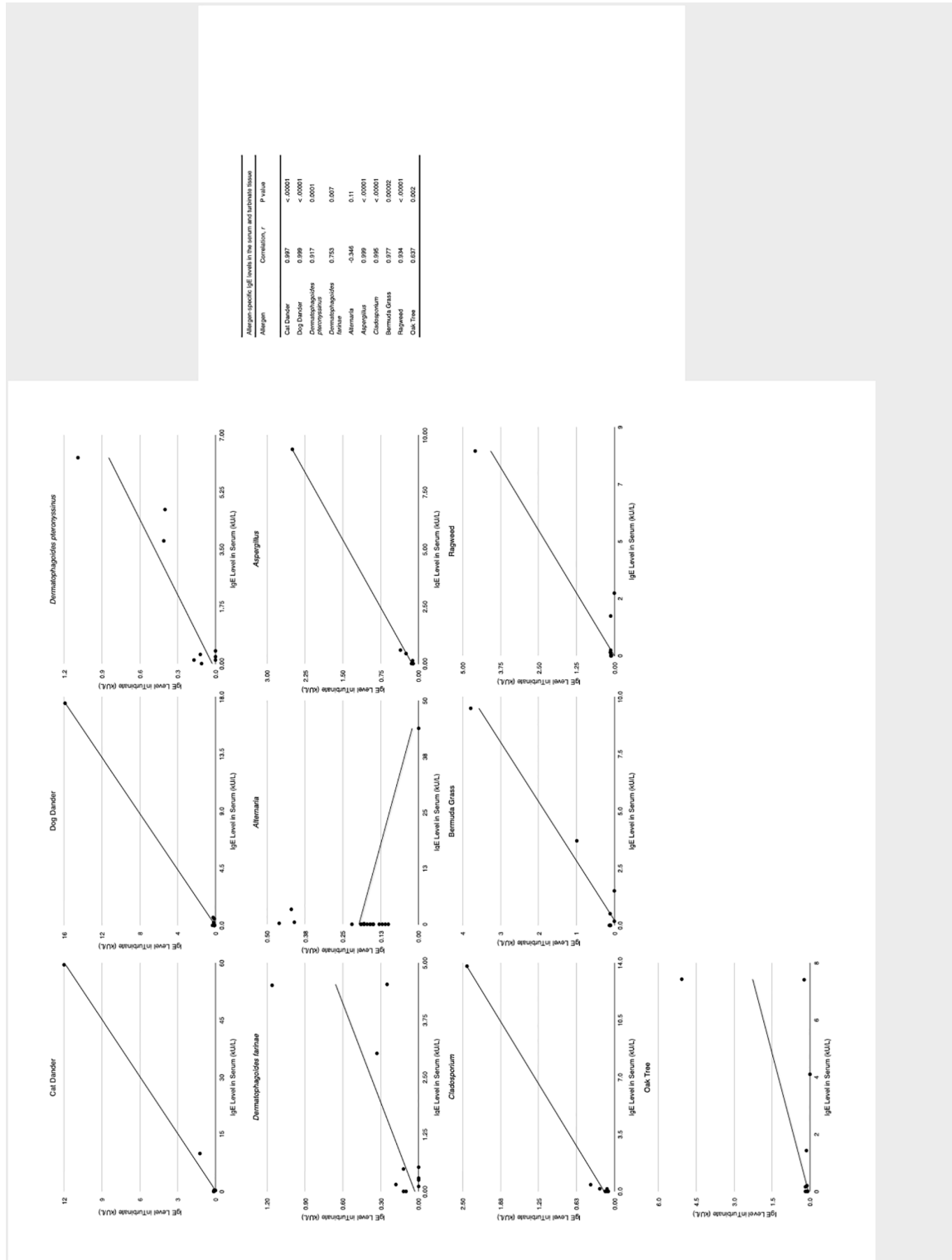


Figure 1. Levels of individual allergen-specific IgE in the serum and inferior turbinate tissue including cat dander, *D. pteronyssinus*, *D. farinae*, *Alternaria*, *aspergillus*, *Cladosporium*, *Bermuda grass*, and oak tree.

our patients. Ota et al described similar results in their study of adult patients with AR. They reported a significant correlation of both total IgE and cedar pollen-specific IgE in the turbinate tissue and serum of 11 patients. Yet, no correlation was found between nasal tissue IgE and serum IgE for house dust and mites.¹⁵ The strong correlations found in our study do not suggest production of allergen-specific IgE in the turbinate tissue to be independent of systemic IgE production, but rather highly connected, as suggested by the aforementioned study.

There are several limitations to this study. First, our study was limited by the small number of study subjects. Another limitation is the fact that no standardized method for collection of inferior turbinate tissue and processing for IgE analysis exists. Thus, it is unknown whether the cut-off level of 0.35 kU/L, as is used in serum IgE testing, is appropriate for data analysis. Additionally, our study did not include an asymptomatic control group. It would be difficult to rationalize obtaining turbinate tissue from asymptomatic pediatric patients, so a different study design using a less invasive method for obtaining tissue samples may be necessary for those experiments.

Conclusion

These study results show no evidence of a local allergic response in the nasal mucosa in our group of pediatric patients with rhinitis symptoms and negative serum testing. Instead, we found local levels of IgE to be present in the nasal tissue in only those with AR. Certain allergen-specific IgE antibodies in the nasal mucosa seem to be highly associated with those in the serum, based upon the significant correlations we found between the two.

Authors' Note

Charles Elmaraghy is a consultant for Smith and Nephew.

Declaration of Conflicting Interests

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ORCID iDs

Alessandra Bliss  <https://orcid.org/0000-0001-6450-0862>

Charles A Elmaraghy  <https://orcid.org/0000-0002-1890-2876>

Supplemental Material

Supplemental material for this article is available online.

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