

Prevalence of antigen-specific immunoglobulin E on mucosal brush biopsy of the inferior turbinates in patients with nonallergic rhinitis

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Background: This study investigates the prevalence of local, antigen-specific immunoglobulin E (IgE) from mucosal brush biopsy (MBB) of the inferior turbinates in people diagnosed with chronic, idiopathic, nonallergic rhinitis (NAR) based on negative skin and/or in vitro testing.

Methods: A standard cytology brush was used to harvest epithelial cells from the inferior turbinates of 20 adults. These cells were then processed and tested for the presence of total and antigen-specific IgE to 9 common aeroallergens using immunofluorescence. The relationships between detectable IgE and quality of life (QOL), self-reported seasonal symptoms and season of specimen collection were determined.

Results: Antigen-specific IgE for at least 1 antigen was detected on MBB in all of 20 (100%) study participants with a mean of approximately 3 sensitizations per participant. IgE to cockroach was present in 18 of 20 (90%) participants. There was no significant association noted between QOL scores or self-reported seasonal symptoms and the presence of specific IgE to any of the study antigens, although the presence of white oak and ragweed IgE was significantly higher in patients tested during the pollen season.

Conclusion: This study demonstrated that, using MBB of the inferior turbinates, antigen-specific IgE to at least 1 air-

borne allergen is detectable in 100% of the idiopathic, NAR study population. This rate of sensitization is notably higher than previous reports, suggesting that the prevalence of atopic disease in the general population may be higher than current estimates. Testing for local sensitization should be considered as part of the complete evaluation for atopic disease. © 2014 The Authors. International Forum of Allergy & Rhinology published by Wiley Periodicals, Inc., on behalf of ARS-AAOA, LLC.

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Key Words:

allergy testing; mucosal brush biopsy; nonallergic rhinitis; inferior turbinate; IgE

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It has been estimated that there are approximately 80 million people in the United States with chronic rhini-

tis (CR), characterized by inflammation of the sinonasal mucosa and clinical symptoms, including congestion, rhinorrhea, sneezing, pruritis, and postnasal drainage.^{1,2} The differential diagnosis for nonallergic rhinitis (NAR) includes rhinitis medicamentosa, gustatory rhinitis, hormone-induced rhinitis, infectious rhinitis, nonallergic rhinitis eosinophilia syndrome (NARES), occupational rhinitis, senile rhinitis, atrophic rhinitis, cerebrospinal fluid leak and vasomotor rhinitis. However, even after a complete evaluation, approximately one quarter of people with CR remain in the idiopathic, NAR category based on the absence of antigen-specific immunoglobulin E (IgE) on skin or in vitro testing.³

It has previously been shown that antigen-specific IgE can be produced in the sinonasal mucosa of people with seasonal and perennial allergic rhinitis (AR), and increases

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rapidly in the epithelium and nasal secretions of people with AR who are challenged with an antigen to which they are sensitized.^{4–7} It has also been demonstrated that locally-produced IgE can be present in nasal secretions even though skin testing⁸ and in vitro testing⁹ are negative. Based on these findings, it has been suggested that people diagnosed with idiopathic NAR may actually have allergic sensitization exclusively in the local region where symptoms are most active. This is known as local allergic rhinitis (LAR).¹⁰

The purpose of this study is to investigate the prevalence of LAR to 9 common airborne allergens in the sinonasal mucosa of 20 symptomatic adults diagnosed with idiopathic NAR based on negative skin and/or in vitro testing. Locally-present, antigen-specific IgE was measured using mucosal brush biopsy (MBB), a minimally-invasive technique that does not require antigen challenge. It has been previously demonstrated that MBB of the inferior turbinates is able to detect antigen-specific IgE in people with AR and positive skin prick testing (SPT).¹¹ The percentage of study participants with detectable antigen-specific IgE was calculated along with the prevalence of positive IgE to each of the study antigens. The associations between local sensitization and quality of life (QOL) scores, self-reported seasonal symptoms, and the season of specimen collection were also determined.

Subjects and methods

Study population

Approval for this study was obtained from the Institutional Review Board of Weill Cornell Medical College, New York City (Protocol #1206012451). Inclusion criteria for the study included a clinical history of idiopathic NAR, age 18 years or greater with negative skin and/or in vitro testing. People with a history of allergy immunotherapy, nasal polyps, current pregnancy, chronic decongestant spray use, or chronic/active infection were excluded from the study. Nine common airborne antigens were used for this study: white oak, Timothy grass, ragweed, cat, dog, *Alternaria*, *Aspergillus*, *D. farinae*, and cockroach.

SPT for between 22 and 30 airborne antigens was performed along with histamine as a positive control and 50% glycerin as a negative control. If no positive reactions (>3 mm wheal diameter) were detected, intradermal testing using 0.02 mL of a #2 dilution (1:500) of the study antigens was performed. If any positive reactions (>6 mm wheal diameter) were detected, the person was excluded from the study. People who were nonreactors to histamine, those who requested in vitro testing or those who were determined to be better candidates for in vitro testing underwent ImmunoCAP serum analysis (Thermo Fisher, Portage, MI) for a panel of 37 airborne and food allergens, including the study antigens. Any person with at least 1 positive antigen-specific IgE level (>0.35 kU/L) in the panel was excluded from the study. All potential study participants

were counseled about the research protocol and informed consent was obtained prior to enrollment.

Upon enrollment, study participants completed the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).¹² Each item was rated on a scale of 0 to 6 (0 = not troubled, 6 = extremely troubled). The overall score was calculated by determining the mean of all 28 responses, and a higher score indicated higher impact on QOL. If a response in any of the health domains was omitted, no overall RQLQ score was calculated for that participant. Overall scores were then divided into low impact on QOL (0.0–3.00) and high impact on QOL (3.01–6.00).

For the analysis of self-reported seasonal symptoms, the study antigens were divided into 5 antigen categories: Pollen (white oak, Timothy grass, and ragweed), mold (*Alternaria* and *Aspergillus*), pet dander (cat and dog), dust mite (*D. farinae*), and cockroach. Self-reported seasonal symptoms were divided into perennial symptoms only and seasonal symptoms with or without perennial symptoms. For the season of specimen collection, participants were divided into 2 groups: October–February, corresponding to the non-pollen season, and March–May, corresponding to the pollen season. All testing was performed at a single institution, Weill Cornell Medical College.

MBB

Prior to MBB, the nasal cavity was decongested and anesthetized on both sides with topical 2% lidocaine and 1% phenylephrine. After waiting 5 minutes, a 7.75-inch cytology brush (Aeromed, Glastonbury, CT) was inserted along the medial surface of the anterior third of the inferior turbinate as described.¹¹ While avoiding direct pressure on the septum, the brush was rotated and moved back and forth approximately 10 times. After the procedure was repeated on the opposite side with a separate brush, the brushes were rinsed for 2 minutes in phosphate buffered saline (PBS) to extract mucus and epithelial cells. No adverse events occurred during the procedure and none were reported afterward.

Measurement of IgE and total protein

The suspensions of epithelial cells were stored in sterile, polypropylene tubes and frozen immediately after harvest. After thawing, the cells were lysed using an ultrasonicator (Branson Digital Sonifier, Danbury, CT) at 45% amplitude for 2 minutes at 15-second intervals. Up to 4 additional 15-second pulses were performed until the lysates appeared clear and Trypan Blue exclusion test demonstrated that no viable cells were present. Total protein concentration for the lysates was determined using a BCA assay (Thermo Scientific, Rockford, IL). One-milliliter samples of each lysate were then sent frozen to a reference laboratory (IBT Laboratories, Lenexa, KS) for ImmunoCAP analysis to determine total IgE levels as well as antigen-specific IgE levels for the 9 study antigens.

TABLE 1. Patient demographics

Age, years, mean (range)	38.0 (23–59)
Males, n (%)	2 (10)
Females, n (%)	18 (90)
Perennial symptoms only, n (%)	7 (35)
Seasonal $\pm$ perennial symptoms, n (%)	13 (65)
SPT + ID testing, n (%)	2 (10)
In vitro testing, n (%)	18 (90)

ID = intradermal; SPT = skin prick testing.

TABLE 2. Patient symptoms

Symptom	Number of patients (%)
Congestion	20 (100)
Rhinorrhea	17 (85)
Sneezing	17 (85)
Itching	18 (90)
Eye symptoms	15 (75)
Wheezing/chest tightness	6 (30)
Postnasal drip	16 (80)

Statistical analysis

Data are presented as mean values $\pm$ standard error of the mean (SEM). Because of the small study population, Fisher's exact testing was used to test the strength of association between the presence of IgE to each of the study antigens and QOL scores, presence of self-reported seasonal symptoms, and season of specimen collection. Two-tailed p values were calculated using online statistical software and a value of $p < 0.05$ was considered statistically significant.¹³

Results

Study population

The demographic characteristics of the 20 study participants are presented in Table 1. Twelve participants (60%) underwent primary in vitro testing, whereas the other 8 (40%) underwent SPT. Six of the SPT participants (75%) were nonreactors to histamine and subsequently underwent in vitro testing. The prevalence of symptoms is shown in Table 2.

Antigen-specific IgE, total IgE, and total protein

All 20 (100%) study participants had detectable IgE to at least 1 of the study antigens from the sinonasal mucosa. The mean number of positive antigens for each participant was 3.15 ± 0.39 (range, 1–8). Overall, 63 (35%) tests were positive for antigen-specific IgE. The prevalence of positive IgE for each of the study antigens is presented in Table 3.

TABLE 3. Frequency of positive MBB testing by test antigen

Antigen	Number of positive tests (%)
White oak	13 (65)
Timothy grass	2 (10)
Ragweed	14 (70)
Cat	1 (5)
Dog	5 (25)
<i>Alternaria</i>	0 (0)
<i>Aspergillus</i>	8 (40)
<i>D. farinae</i>	2 (10)
Cockroach	18 (90)
Total	63 (35)

MBB = mucosal brush biopsy.

All positive reactions were class 0/1 (0.10–0.35 kU/L). The mean total IgE for each MBB sample was 4.75 ± 0.43 IU/ml (range, 3–10) and the mean total protein for each sample was 1.85 ± 0.09 mg/mL (range, 1.20–2.47). The mean total IgE corrected for total protein was 432.72 ± 36.14 mIU/mg.

QOL scores

Seven (35%) participants were placed into the low impact on QOL group, while 10 (50%) were placed into the high impact on QOL group. Three (15%) participants did not have their RQLQ scored because items were left out. The mean overall RQLQ score was 3.00 ± 0.35 (range, 0.29–5.07). As shown in Figure 1, there was no significant association noted between the presence of IgE to any of the study antigens and QOL scores.

Self-reported seasonal symptoms

Seven (35%) participants reported perennial symptoms only, 1 (5%) reported seasonal symptoms only, and the other 12 (60%) participants reported perennial symptoms with seasonal exacerbation. As shown in Table 4, there was no significant association between the presence of IgE to antigens in any of the antigen categories and self-reported seasonal symptoms.

Season of specimen collection

Nine (45%) participants were tested during the months of October, 2012 to February, 2013, whereas 11 (55%) participants were tested during the months of March–May, 2013, which corresponded to the beginning of the pollen season in New York City. The results of Fisher exact testing are shown in Figure 2. There was a significant association noted between the presence of IgE to both white oak ($p = 0.04$) and ragweed ($p = 0.02$) and specimen collection during the pollen season. For all other test antigens, there was

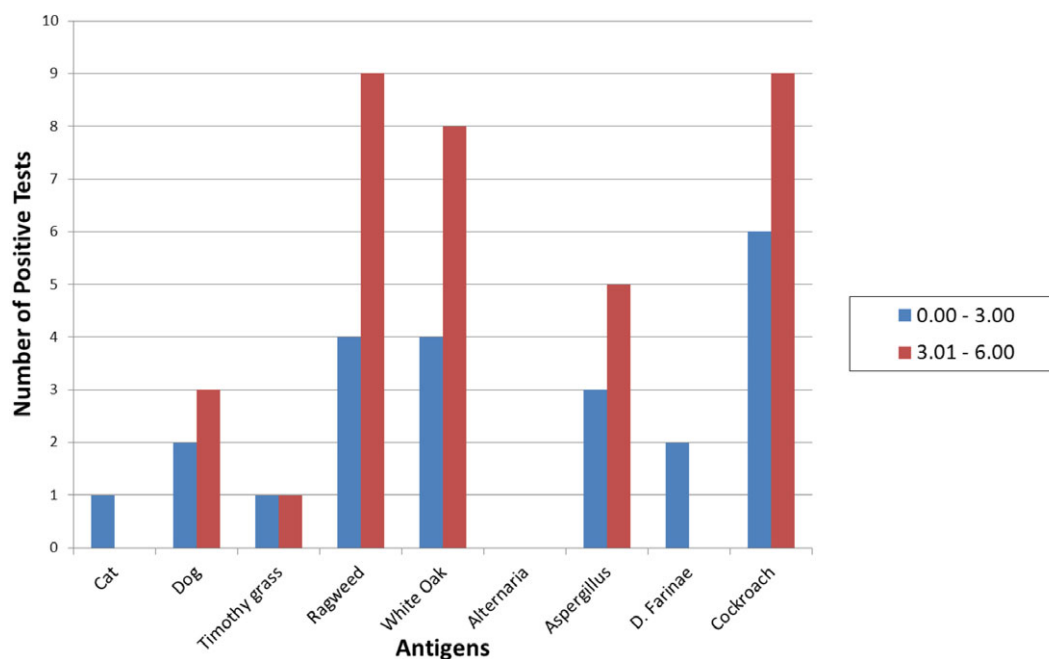


FIGURE 1. Fisher's exact testing for association between the presence of antigen-specific IgE to the test antigens and quality of life scores. * $p < 0.05$. IgE = immunoglobulin E.

TABLE 4. Fisher's exact testing for association between positive MBB for each test antigen category and reported seasonal symptoms^a

Antigen category	P	S ± P	MBB +	MBB –	<i>p</i>
Pollen (WO, TG, RW)	7	13	14	6	0.61
Mold (<i>Alternaria</i> and <i>Aspergillus</i>)	7	13	8	12	0.36
Pet dander (cat and dog)	7	13	5	15	1.0
Dust mite (<i>D. farinae</i>)	7	13	2	18	1.0
Cockroach	7	13	18	2	0.52

^aStatistically significant values are in bold.

MBB = mucosal brush biopsy; P = perennial symptoms; RW = ragweed; S = seasonal symptoms; TG = Timothy grass; WO = white oak.

no significant association between the presence of antigen-specific IgE and the season of specimen collection.

Discussion

All of the study participants had detectable, antigen-specific IgE on MBB, which is higher than previous reports that used nasal allergen provocation testing (NAPT) to detect local sensitization. Using NAPT, the prevalence of LAR in people with a diagnosis of NAR ranges between 47% and 63% in patients with perennial^{14,15} and seasonal^{16,17} symptoms. Using homogenized nasal mucosa, Ohashi et al.¹⁸ detected antigen-specific IgE in all of 12 (100%) patients diagnosed with NAR based on negative skin and in vitro testing. This suggests that the sampling of tissue may be more sensitive for the detection of locally-present IgE than provocation testing in patients with idiopathic NAR.

MBB was chosen for this study because antigen-specific IgE and IgE+ cells are known to exist in the epithelium and subepithelium of the inferior turbinates in people with AR, and mast cell activation occurs in this region as well.^{19–22} MBB, which harvests epithelial cells, is less invasive and easier to perform in the outpatient setting compared to surgical biopsy, which also harvests subepithelial and fibrovascular tissue. In addition, MBB does not involve the discomfort and risks associated with antigen challenge, and the results are less subjective when compared to NAPT.²³

It is logical that 90% of study participants demonstrated antigen-specific IgE to cockroach, considering that most of our study participants either live or have lived in an inner-city dwelling with cockroach infestation. The fact that Timothy grass had a much lower rate of sensitization than either white oak or ragweed (10% vs 65% and 70%, respectively) possibly reflects the typical pattern of sensitization in the study region and the fact that no participants were recruited during the grass pollination season. It was surprising, however, that certain antigens, such as cat, *Alternaria*, and *D. farinae* had such a low (10% or under) prevalence of locally-detectable IgE. One possible explanation for this is that smaller antigens may contact the posterior nasal cavity, pharynx, and lower airway more easily than larger antigens and, as such, produce less local sensitization on the area of the inferior turbinates where MBB was performed. Alternatively, those 3 antigens may be so common that skin or in vitro testing was more likely to be positive than for the other study antigens, causing those potential study participants with sensitization to them to be excluded from the study.

In our study, no significant association was noted between the presence of IgE to a particular antigen and total

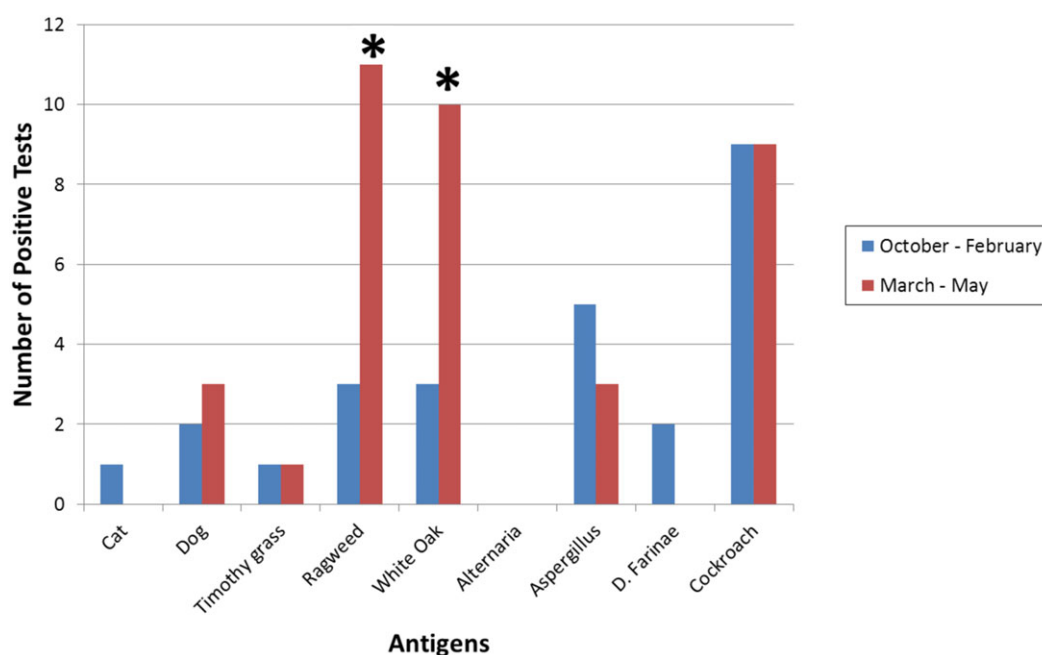


FIGURE 2. Fisher's exact testing for association between the presence of antigen-specific IgE to the test antigens and the season of specimen collection. * $p < 0.05$. IgE = immunoglobulin E.

RQLQ score. Previous studies have reported that disease severity, in relation to nasal congestion and rhinorrhea, is comparable between patients with AR and NAR, so the RQLQ results were not surprising.²⁴ Likewise, there was no significant association between the presence of IgE in any of the antigen categories and self-reported seasonal exacerbation of symptoms. It was initially expected that study participants with detectable, antigen-specific IgE in the mold and pollen groups would be more likely to report seasonal exacerbation of symptoms, but perhaps it was difficult for some individuals to distinguish this subtle difference in the context of chronic, moderate to severe symptoms.

There was a significant association between the spring collection season and the detection of antigen-specific IgE for both white oak and ragweed. This may reflect the self-selection of seasonal AR patients at that time of the year, but also raises the question of whether local levels of antigen-specific IgE vary throughout the year based on the exposure to that antigen. The finding that ragweed was also significantly elevated during the spring argues against that, but the question remains whether or not testing should be done during multiple times of the year to detect a pattern of sensitization which may be unique to the individual. Ono et al.²⁵ demonstrated that levels of specific IgE to Japanese cedar in tears increased as the pollination season proceeded, but decreased once the season was over.

It has been demonstrated that local testing for antigen-specific IgE in symptomatic regions may reveal sensitizations not found on systemic testing (in vitro) or local testing in asymptomatic regions.^{10,26} In the Japanese cedar study, local IgE levels increased prior to serum IgE levels, whereas serum levels remained elevated, even during the non-pollen

season.²⁵ Zhang et al.²⁷ studied 83 children without CR who failed medical management of adenotonsillar hypertrophy with obstructive sleep apnea. Of the 32 (38.5%) patients who were serum negative for airborne and/or food allergens, 36% had antigen-specific IgE in the adenoid tissue, whereas 43.8% had antigen-specific IgE in the tonsil tissue. Reisacher and Cohen²⁸ determined that MBB of the oral cavity mucosa detected peanut-specific IgE in 100% of people with oral cavity symptoms after consuming that antigen, vs a 50% detection rate of peanut-specific IgE with in vitro testing.²⁸

Current data support the fact that IgE-mediated sensitization to allergens, in genetically predisposed individuals, occurs initially in the regions of the aerodigestive tracts where contact is most likely to be made.²⁹⁻³¹ Depending on the pattern of exposure of the person to a particular antigen over time, subsequent sensitizations may become evident in other local regions as well. When patients with LAR for grass pollen underwent subcutaneous immunotherapy (SCIT), 40% of patients became positive for grass pollen on SPT after 6 months, presumably related to the increase in skin and/or systemic exposure.³² Ongoing studies will help determine the level of locally-present, specific IgE required to produce symptoms in a given region, as well as the level required to produce systemic positivity. To reach this goal, it will also be necessary to identify more sensitive methods of detecting low levels of IgE in local tissues where atopic disease is common.

Based on the current literature, and supported by the current study, a complete workup for individuals suspected of having atopic disease should include local testing at 1 or more symptomatic regions, particularly when the clinical condition is incongruent with the results of skin or in

vitro testing. The European Academy of Allergy and Clinical Immunology (EAACI) defines “atopy” as “a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis.”³³ As such, patients with evidence of antigen-specific IgE in local tissues, even in the absence of systemic sensitization, would fall under this definition. The prevalence of atopic disease is currently estimated at 20% of the world’s population.^{34–37} However, because local sensitization has not been factored into this estimate, the number is likely higher.

This study demonstrated that MBB of the inferior turbinates is able to detect locally-present, antigen-specific IgE in the NAR population. However, the clinical relevance of this novel testing method has yet to be determined. Local sensitization, just like systemic sensitization, must always be considered in the context of the patient’s symptoms. Potentially, a more concise list of relevant sensitizations could focus environmental control strategies and might also provide guidance for the administration of immunotherapy. Although it is important to determine the sensitivity and specificity of local IgE testing, currently there is no “gold

standard” for testing in the aerodigestive tract and levels of antigen-specific IgE in these various regions in asymptomatic individuals are unknown. Larger populations of pediatric and adult patients with different atopic diseases need to be included in upcoming studies to determine the best region or regions to perform local testing for each individual.

Conclusion

Using MBB of the inferior turbinates, the prevalence of local, antigen-specific IgE in study participants diagnosed with idiopathic NAR was found to be notably higher than previously reported. Ongoing work in this area will focus on the relationship between local sensitization and symptomatology, as well as the utility of this novel test in the diagnosis of allergic disease. ☯

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