

Nasal mucosal brushing as a diagnostic method for allergic rhinitis

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ABSTRACT

Background: Allergen specific immunoglobulin E (spIgE) in the nasal mucosa is a biomarker for local allergic rhinitis. Inferior turbinate tissue biopsy is a sensitive method to detect nasal spIgE but is invasive. Nasal brushing is a relatively noninvasive method to detect nasal spIgE that may be of comparable diagnostic utility.

Objective: To assess the performance of nasal brushing to obtain a nasal spIgE sample compared with an inferior turbinate tissue biopsy among patients who underwent turbinate surgery.

Methods: A diagnostic cross-sectional study that involved participants who were undergoing turbinate surgery was performed. Nasal brushing, inferior turbinate tissue biopsy, blood collection, and skin-prick test (SPT) were performed perioperatively and tested for house-dust allergens. A receiver operating curve was used to assess the performance of the nasal brushings to obtain nasal spIgE samples compared with the inferior turbinate tissue biopsy. The diagnostic utility of nasal brushings of spIgE compared with serum spIgE testing and SPT was also assessed.

Results: A total of 157 patients (41.61 ± 14.83 years; 37.6% women) were included. Nasal brushing was an excellent method to sample for nasal spIgE compared with inferior turbinate tissue biopsy (Area under curve (AUC) 0.87 [95% confidence interval {CI}, 0.81–0.93], $p < 0.01$). Positive house-dust allergen spIgE results of nasal brushings was defined as > 0.1 kUA/L. Nasal brushings for spIgE sampling was also able to predict the presence of serum spIgE (AUC 0.93 [95% CI, 0.89–0.97], $p < 0.01$) and SPT (AUC 0.80 [95% CI, 0.72–0.87], $p < 0.01$).

Conclusion: Nasal brushing constituted an easy and relatively noninvasive method to sample nasal epithelium. This sampling technique was comparable with an inferior turbinate tissue biopsy and may be developed as a diagnostic tool for the diagnosis of local allergic rhinitis.

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Allergic rhinitis (AR) is defined as immunoglobulin E (IgE) mediated inflammation of the nasal mucosa.¹ This is determined by proving the presence of allergen specific IgE (spIgE), detected through standard tests, which are the serum spIgE test and skin-prick test (SPT).¹ However, these tests have flaws because patients with local AR² (LAR) have a well-defined local allergic nasal response despite a negative serum allergen spIgE test and/or SPT results.³ It was

reported in a systematic review that allergen reactivity can still occur in 26.5% of those without evidence of atopy.⁴ This has been termed “entropy” or “local allergy.”⁵ When this occurs in the nasal cavity, the term LAR is commonly used.⁶ It is important to detect LAR because it responds to immunotherapy.⁷

LAR is thought to occur due to local spIgE production in the nasal mucosa. This locally produced spIgE binds to resident mast cells and is released into nasal secretions.⁸ Thus, nasal cavity sampling for spIgE is believed to be a more accurate representation of both AR and LAR because it is the primary site that comes into contact with allergens. The direct inferior turbinate tissue biopsy samples the nasal epithelium as well as the submucosal layer.⁹ Studies reported this to be a

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sensitive method to sample for nasal sIgE.^{10,11} The presence of inferior turbinate tissue sIgE (>0.1 kUA/L) was found to be a predictive test for AR with 90% sensitivity and 88% negative predictive value.¹¹ In an early study, Ohashi *et al.*,¹⁰ reported that allergen sIgE from inferior turbinate tissue was a highly sensitive marker (100%) of AR. Other studies that used tissue sIgE in nasal mucosa¹² and adenoids¹³ also reported high sensitivity. Unfortunately, this method is invasive and not suitable as a routine diagnostics test. However, it is useful as a local reference test to assess the performance of less-invasive nasal sampling methods.

Nasal brushing by using a cytology brush is a practical, relatively noninvasive, and well-tolerated sampling alternative. This method samples the nasal epithelium and can be easily performed in daily clinic practice. Nasal brushings have also been found to result in a higher protein yield compared with the nasal curette and dental brush.¹⁴ It is an attractive option for nasal allergy testing, especially when LAR is suspected. The use of nasal brushings to detect allergen sIgE was described in several small case series, but its performance to sample nasal sIgE was not assessed.^{15–17} Another study assessed nasal brushings for sIgE sampling to predict AR (determined by positive serum sIgE and/or SPT result) but did not take into account locally produced sIgE.¹⁴ The performance of nasal brushings as a tool to obtain an sIgE sample should be assessed together with a known sensitive method for sampling the nasal mucosa sIgE. This is to ensure that locally produced sIgE have been included; however, current^{14–17} literature mostly focused on comparisons with standard allergy tests. The aim of this study was to assess the effectiveness of nasal brushings to obtain nasal sIgE samples compared with the inferior turbinate tissue biopsy. The diagnostic utility of nasal brushings for sIgE was also compared with the current diagnostic tool for AR, which is the serum sIgE test and SPT. This method of nasal sampling needs to be formally assessed because it has the potential to be developed as a simple, relatively noninvasive tool to diagnose LAR.

METHODS

For this cross-sectional diagnostic study, recruitment was performed at tertiary referral centers between September 2015 and June 2017. Appropriate ethics approval was obtained before study commencement (HREC/15/SVH/24), and the patients provided informed consent.

Study Population

Consecutive adults (≥ 18 years old) who were undergoing inferior turbinate reduction surgery as an isolated intervention or as part of another procedure were

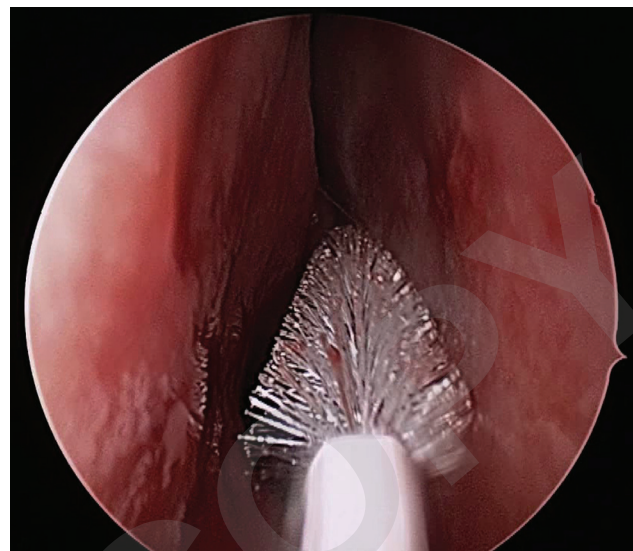


Figure 1. Nasal endoscopic view of cytology brush sampling. Representative endoscopic image of cytology brush being inserted into the right nasal cavity along the medial edge of the inferior turbinate and septum to sample the mucosal epithelium.

recruited. Patients with known systemic conditions thought to affect the nasal mucosa, including immunodeficiency, vasculitis, cystic fibrosis, or granulomatous disease, were excluded. All the patients completed a questionnaire before surgery. Nasal symptoms (duration [years], type [intermittent or persistent]), and allergic comorbidities (asthma, eczema, allergic conjunctivitis, family history of atopy) were assessed. Nasal brushing and blood samples were collected with the patient under general anesthesia before commencement of surgery, and an inferior turbinate tissue biopsy was taken during surgery. SPT was performed within 6 months of surgery.

Nasal Brushings

The patients were subjected to nasal brushings of both nasal cavities by using a cytology brush (EndoscanPlus, Medico, Melbourne, Australia) (Fig. 1). The nasal brushings were performed with the patient under general anesthesia before the surgical procedure and nasal preparation (with local anesthetic and vasoconstrictor). Cytology brushings samples were placed in a Cryovial (Greiner Bio-one, Frickenhausen, Germany) and snap frozen in liquid nitrogen, then processed for nasal sIgE as previously described.¹⁴ Briefly, after thawing, the brushings suspensions were sonicated (Ultrasonic processor UTR200 sonoreactor; Hielcher, Teltow, Germany) to allow cell lysis (45% amplitude, 10-second burst with 10-second intervals), and cell debris was removed by centrifugation (3000 rpm, 10 minutes, 4°C) and stored at -70°C until further processing.

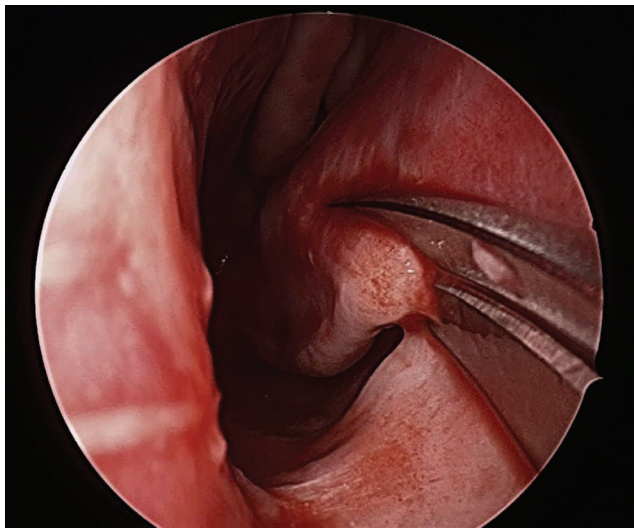


Figure 2. Nasal endoscopic view of a tissue biopsy. A representative endoscopic image of a tissue biopsy performed in the right nasal cavity by using a curved iris scissor to cut the anterior edge of the inferior turbinate.

Inferior Turbinate Tissue Biopsy

After nasal decongestion by using adrenaline 1:1000, the anterior portion of the inferior turbinate head was cut by using curved scissors (Fig. 2) and snap frozen in vapor-phase liquid nitrogen. Tissues were suspended in 1 mL phosphate buffered saline (PBS), 40 μ L of protease inhibitor (cOmplete Protease Inhibitor Cocktail; Merck KGaA, Darmstadt, Germany per 0.05 g of tissue (weighed in the frozen state) and homogenized (10,000 rpm, 30 seconds) by using a mechanical Homogenizer (B. Braun, Melsungen, Germany). The samples were then sonicated, centrifuged, and stored by using the same methods for the nasal brushings.¹⁴

Immunoassay Analysis

Thawed cytology brushing supernatants, tissue homogenates, and serum samples were analyzed for the presence of house-dust allergen mix sIgE by using an automated immunoassay (ImmunoCAP, Phadia 250, Thermo Fisher Scientific, Waltham, Massachusetts) by following the standard protocol for serum testing set by the laboratory. This mix contained *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blattella germanica* (cockroach). The lowest threshold for detection was 0.01 kUA/L. A positive serum sIgE result was defined as a concentration of ≥ 0.35 kUA/L. A positive tissue sIgE result was defined as a concentration value of >0.1 kUA/L. The accuracy of the tissue sIgE threshold to determine AR has been reported elsewhere.¹¹

SPT

SPT was performed to detect sensitization to the individual allergen components of house dust (*D.*

pteronyssinus, *D. farinae*, and *B. germanica*) in 50% glycerin (Western Allergy, Victoria BC, Canada). Both negative control (50% glycerin) and positive control (histamine) were used. A positive SPT result was defined as a wheal diameter of ≥ 3 mm, with a nonreactive negative control, measured after 15 minutes.

Statistical Analysis

All statistics and graphic representations of data were performed by using SPSS version 24 (IBM Corp., Armonk, NY). Receiver operating curves (ROC) were generated to determine the cutoff value (with a high sensitivity based on the coordinates of the curve) for nasal brushing for house-dust sIgE by using inferior turbinate tissue biopsy, serum sIgE, or SPT as the reference test. The sensitivity, specificity, positive likelihood ratio, positive predictive value, diagnostic accuracy, and diagnostic odds ratio were then calculated for each reference test. The sample size was calculated by using a formula by Hajian-Tilaki.¹⁸ The planned sample of 109 participants aimed at a sensitivity of 90%, a margin of error not exceeding 7%, and an α value of 0.05.

RESULTS

There were 157 participants included in this study, age 41.61 ± 14.83 years, and 37.6% were women. There were 75.8% with positive sIgE results in the inferior turbinate tissue, 48.4% with positive serum sIgE results, and 56.6% with positive SPT results for house dust. These patients mainly had persistent symptoms (89%) and had nasal symptoms for > 6 years (69.2%). A positive family history of allergy was reported by 50% of the patients. More than half of the patients (58.4%) reported nasal symptoms that were triggered in a dusty environment. The allergic comorbidities were bronchial asthma (32%), eczema (17.3%), and allergic conjunctivitis (12.8%).

Diagnostic Accuracy of Nasal Brushings

ROC curves were created to assess the performance of the nasal brushings versus inferior turbinate tissue biopsy. The ROC curve defined an excellent overall accuracy for nasal brushings for sIgE to predict a positive inferior turbinate tissue biopsy result (AUC 0.87 [95% CI, 0.81–0.93], $p < 0.01$) (Fig. 3a). The nasal brushing sIgE sample was also able to predict positive standard diagnostic test results for allergy: serum sIgE (AUC 0.93 [95% CI, 0.89–0.97], $p < 0.01$) and SPT (AUC 0.80 [95% CI, 0.72–0.87], $p < 0.01$) (Fig. 3, b and c).

A concentration cutoff value of >0.1 kUA/L was chosen to define a positive nasal brushing for sIgE

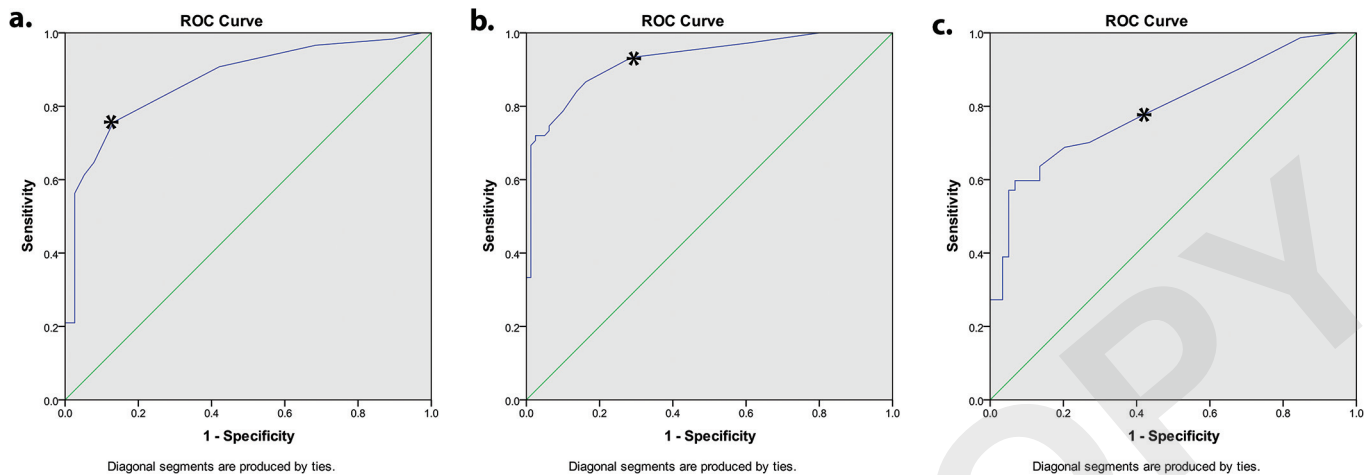


Figure 3. Nasal brushing house-dust specific immunoglobulin E (spIgE) receiver operating curve (ROC). ROC was applied from nasal brushing of house dust spIgE among patients with rhinitis compared with results of (a) inferior turbinate tissue, (b) serum spIgE, and (c) skin-prick test house-dust spIgE. The selected cutoff (>0.10 kUA/L) is depicted by (*).

Table 1 A 2 × 2 contingency table compares the number of positive tests in nasal brushing sample and inferior turbinate tissue for house-dust allergen				
		Tissue House-Dust spIgE Result		Total
		Positive (>0.1 kUA/L)	Negative (≤0.1 kUA/L)	
Nasal Brushings, house-dust spIgE result	Positive (>0.1 kUA/L)	90	5	95
	Negative (≤0.1 kUA/L)	29	33	62
Total		119	38	157

spIgE = Specific immunoglobulin E.

Table 2 A 2 × 2 contingency table compares the number of positive tests in nasal brushing sample with serum spIgE for house-dust allergen				
		Serum spIgE Result		Total
		Positive	Negative	
Nasal brushings result, house-dust spIgE	Positive (>0.1 kUA/L)	70	23	93
	Negative (≤ 0.1 kUA/L)	5	57	62
Total		75	80	155*

spIgE = Specific immunoglobulin E.
*Two incomplete serum assessments.

result depicted by the asterisk (*) (Fig. 3). The diagnostic accuracy calculated from the 2 × 2 table (Table 1) showed that a positive nasal brushing for spIgE result had a sensitivity of 75.6% and a specificity of 86.8% when compared with tissue spIgE. The diagnostic accuracy of nasal brushing for spIgE compared with serum specific IgE and SPT is depicted in the 2 × 2 tables (Tables 2 and 3). Nasal brushings for spIgE (>0.1 kUA/L) had a high sensitivity (93.3% and 77.9%) but low specificity (71.3% and 57.6%) when compared with serum spIgE and SPT results (Table 4).

DISCUSSION

In this study that used house-dust allergen, we demonstrated that nasal brushing was a useful tool for sampling allergen spIgE and was comparable with an inferior turbinate tissue biopsy (Area under curve (AUC) 0.87 [95% CI, 0.81–0.93], $p < 0.01$), and had similar predictive accuracy compared with serum spIgE (AUC 0.93 [95% CI, 0.89–0.97], $p < 0.01$) and SPT (AUC 0.80 [95% CI, 0.72–0.87], $p < 0.01$). A nasal brushing with an spIgE concentration of >0.1 kUA/L was both sensitive and specific to predict a pos-

Table 3 A 2 × 2 contingency table compares the number of positive test in nasal brushing sample with SPT for house-dust allergen

		SPT Result		Total
		Positive	Negative	
Nasal brushings result, house-dust spIgE	Positive (>0.1 kUA/L)	60	25	85
	Negative (≤ 0.1 kUA/L)	17	34	51
Total		77	59	136*

SPT = skin-prick test.

*Twenty-one incomplete SPTs.

Table 4 Diagnostic accuracy of nasal brushing for house-dust spIgE (>0.1 kUA/L) to determine allergic rhinitis: Positive nasal brushing spIgE values were compared with inferior turbinate tissue biopsy, serum spIgE, and SPT

Nasal Brushings (>0.1 kUA/L)	Inferior Turbinate Tissue (>0.1 kUA/L)	Serum spIgE (≥0.35 kUA/L)	SPT Result (≥3 mm)
Area under the curve (95% CI)	0.87 (0.81–0.93)	0.93 (0.89–0.97)	0.80 (0.72–0.87)
Sensitivity, %	75.6	93.3	77.9
Specificity, %	86.8	71.3	57.6
Positive predictive value, %	94.7	75.3	70.6
Negative predictive value, %	53.2	91.9	66.7
Positive likelihood ratio	5.7	3.3	1.8
Negative likelihood ratio	0.28	0.1	0.4
Diagnostic odds ratio	20.4	36.1	4.8
Diagnostic accuracy, %	78.3	81.9	69.1

spIgE = Specific immunoglobulin E; SPT = skin-prick test; CI = confidence interval.

itive tissue spIgE result and has excellent sensitivity to predict allergy from the serum spIgE sample. Taken together, nasal brushing had the potential to be developed as a tool to diagnose local AR.

House-dust allergens were assessed in this study because it is an important allergen responsible for symptoms of AR and is the main allergen investigated in the literature.⁴ It is the most commonly found allergic sensitization world wide¹⁹ and also in New South Wales, Australia, which is this study's region.²⁰ House-dust spIgE in the nasal mucosa is effectively sampled by using the nasal brushing, and this may be useful to identify patients with LAR toward house dust. Furthermore, the differentiation between the subjects with AR due to house-dust allergy, LAR due to house dust, and non-AR with nonrelevant house-dust sensitization is difficult due to its similar clinical history.⁴ This is in contrast to those with pollen allergy who will have a clear history of seasonality.

Nasal brushing was compared with the inferior turbinate tissue biopsy to assess its ability to sample the nasal spIgE because, as previously mentioned, the inferior turbinate tissue biopsy has been reported to be a sensitive tool to detect the presence of nasal

spIgE.^{10,11,21} However, this invasive method is not suitable for a routine diagnostic test. Nasal brushing was comparable with inferior turbinate tissue biopsy to sample for nasal spIgE. It was comparably as effective as a tissue biopsy to sample nasal spIgE but was easier to perform and far less invasive.

A concentration threshold value of >0.1 kUA/L was chosen as the positive cutoff for nasal brushings for spIgE, which had a 76% sensitivity and 87% specificity to predict a positive tissue spIgE value. This threshold was chosen for the best balance between sensitivity and specificity to detect inferior turbinate tissue spIgE. This was in close agreement with previously reported values. Other studies defined a positive nasal allergen spIgE result as between 0.1 and 0.17 kUA/L. In these studies, the nasal spIgE was sampled by using a variety of techniques, including nasal brushings,^{14,16} scrapings,²² swab,²³ and *in situ* incubation.²⁴

Nasal brushing spIgE was also found to be a sensitive test to detect a positive standard allergy test (94% sensitive to detect a positive serum spIgE result and 78% sensitive to detect a positive SPT result). This was comparable with an inferior turbinate tissue biopsy, which was reported to have 90% sensitivity to diag-

nose AR (when using the standard allergy test).¹¹ However, the specificity was lower to predict a positive standard allergy test result (71% for serum sIgE and 56% for SPT). This lower specificity was likely due to the failure of these systemic tests (serum sIgE and SPT) to detect locally produced nasal sIgE, which gave these tests a substantial false-negative rate.⁴

In this study, we defined a positive threshold for nasal brushing sIgE with good sensitivity to detect both local and systemic sIgE. However, the relationship between the presence of nasal brushing sIgE (>0.1 kUA/L) and the manifestations of AR remains unclear. Three separate case series,^{15–17} reported that 100% of the patients with nasal symptoms had positive sIgE results (≥ 0.1 kUA/L). We also previously showed that patients who were asymptomatic and nonatopic had a median (interquartile range) inferior turbinate tissue sIgE concentration of 0.09 kUA/L (0.08–0.10 kUA/L).¹¹ However, positive nasal sIgE results were demonstrated in healthy subjects without rhinitis,^{15,22} which indicated that, similar to serum sIgE, presence of nasal sIgE does not necessarily indicate clinically expressed AR; this is an area for further research. Although, in this study, nasal brushings were performed with the patient under general anesthesia, this method can be easily translated to clinical practice by administration of local anesthetic spray.

CONCLUSION

Nasal brushings provided an easy, relatively noninvasive diagnostic tool for nasal sampling, which can successfully detect locally produced nasal sIgE compared with the invasive inferior turbinate tissue biopsy. It also compared well with the standard allergy tests, which were the serum sIgE test and SPT. Therefore, nasal brushing for sIgE may potentially be developed as a test to diagnose LAR.

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REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008; 63(Suppl 86):8–160.
2. Rondón C, Canto G, Blanca M. Local allergic rhinitis: a new entity, characterization and further studies. *Curr Opin Allergy Clin Immunol*. 2010; 10:1–7.
3. Rondón C, Romero JJ, LópezS, et al. Local IgE production and positive nasal provocation test in patients with persistent non-allergic rhinitis. *J Allergy Clin Immunol*. 2007; 119:899–905.
4. Hamizan AW, Rimmer J, Alvarado R, et al. Positive allergen reaction in allergic and nonallergic rhinitis: a systematic review. *Int Forum Allergy Rhinol*. 2017; 7:868–877.
5. Powe DG, Bonnin AJ, Jones NS. 'Entopy': local allergy paradigm. *Clin Exp Allergy*. 2010; 40:987–997.
6. Rondón C, Campo P, Togias A, et al. Local allergic rhinitis: concept, pathophysiology, and management. *J Allergy Clin Immunol*. 2012; 129:1460–1467.
7. Rondón C, Campo P, Salas M, et al. Efficacy and safety of D. pteronyssinus immunotherapy in local allergic rhinitis: a double-blind placebo-controlled clinical trial. *Allergy*. 2016; 71: 1057–1061.
8. Smurthwaite L, Walker SN, Wilson DR, et al. Persistent IgE synthesis in the nasal mucosa of hay fever patients. *Eur J Immunol*. 2001; 31:3422–3431.
9. Çomoğlu Ş, Keles N, and Değer K. Inflammatory cell patterns in the nasal mucosa of patients with idiopathic rhinitis. *Am J Rhinol Allergy*. 2012; 26:e55–e62.
10. Ohashi Y, Nakai Y, Kuroki K, et al. Topical immunology of nasal allergy and mucosal IgE antibodies. *Arch Otorhinolaryngol*. 1985; 241:169–174.
11. Hamizan AW, Rimmer J, Alvarado R, et al. Turbinate specific IgE in normal and rhinitic patients. *Am J Rhinol Allergy*. 2019. <https://doi.org/10.1177/1945892418825224>.
12. Ahn CN, Wise SK, Lathers DM, Mulligan RM, Harvey RJ, and Schlosser RJ. Local production of antigen-specific IgE in different anatomic subsites of allergic fungal rhinosinusitis patients. *Otolaryngol Head Neck Surg*. 2009; 141:97–103.
13. Shin SY, Ye YM, Eun YG, Kim SW, Cho JS, and Park HS. Local IgE-mediated hypersensitivity to *Alternaria* in pediatric adenoid tissue. *Int J Pediatr Otorhinolaryngol*. 2012; 76:1423–1428.
14. Saricilar EC, Hamizan A, Alvarado R, et al. Optimizing protein harvest from nasal brushings for determining local allergy responses. *Am J Rhinol Allergy*. 2018; 32:244–251.
15. Reisacher WR. Total and allergen-specific immunoglobulin E in the serum and nasal mucosa of a nonallergic population. *Int Forum Allergy Rhinol*. 2016; 6:618–623.
16. Reisacher WR, Bremberg MG. Prevalence of antigen-specific immunoglobulin E on mucosal brush biopsy of the inferior turbinates in patients with nonallergic rhinitis. *Int Forum Allergy Rhinol*. 2014; 4:292–297.
17. Reisacher WR. Mucosal brush biopsy testing of the inferior turbinate to detect local, antigen-specific immunoglobulin E. *Int Forum Allergy Rhinol*. 2012; 2:69–74.
18. Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. *J Biomed Inform*. 2014; 48:193–204.
19. Bousquet PJ, Chinn S, Janson C, et al. Geographical variation in the prevalence of positive skin tests to environmental aeroallergens in the European Community Respiratory Health Survey I. *Allergy*. 2007; 62:301–309.
20. Kam AW, Tong WW, Christensen JM, Katelaris CH, Rimmer J, and Harvey RJ. Microgeographic factors and patterns of aeroallergen sensitisation. *Med J Aust*. 2016; 205:310–315.
21. Ota Y, Ikemiyagi Y, Sato T, et al. Measuring local immunoglobulin E in the inferior turbinate nasal mucosa in patients with allergic rhinitis. *Allergol Int*. 2016; 65:396–399.
22. Gelardi M, Guglielmi AV, Iannuzzi L, et al. Local allergic rhinitis: entopy or spontaneous response? *World Allergy Organ J*. 2016; 9:39.
23. Ahn JY, Hong SJ, Choi BS. Clinical evaluation of techniques for measuring nasal-specific immunoglobulin E in pediatric patients. *J Korean Med Sci*. 2017; 32:2005–2008.
24. Campo P, Del Carmen Plaza-Seron M, Eguiluz-Gracia I, et al. Direct intranasal application of the solid phase of ImmunoCAP increases nasal specific immunoglobulin E detection in local allergic rhinitis patients. *Int Forum Allergy Rhinol*. 2018; 8:15–19. □

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