

Mucosal brushings for nasal specific IgE to predict house dust mite driven allergic rhinitis

Aneeza W. Hamizan,¹ Raquel Alvarado,² Khaizurin Tajul Arifin,³ Farah Dayana Zahedi, Ng Chong Sian,¹ Anna Fariza Jumaat,¹ Salina Husain,¹ Richard Harvey^{2,4}

Abstract

Background: Skin prick testing and serological identification of allergen specific immunoglobulin E (spIgE) are standard tests for allergic rhinitis but can only identify systemic responses. In contrast, nasal allergen challenge (NAC), directly assess localized nasal mucosal reactivity, but is time consuming. Identification of spIgE from nasal brushings (nasal spIgE) is an alternative technique.

Objective: This study aimed to determine the diagnostic performance of nasal spIgE compared to NAC in order predict house dust mite (HDM) driven AR.

Methods: A diagnostic cross-sectional study involving adult rhinitis patients was performed. Sensitization to HDM allergens (*Dermatophagoides pteronyssinus* (DP), *Dermatophagoides farina* (DF) were assessed serologically and/or skin prick test, nasal brushing and NAC. Patients with both positive systemic test and NAC were defined to have HDM driven AR, while patients with a positive systemic test and negative NAC were defined to have non-clinically relevant HDM sensitization. The performance of nasal spIgE to predict positive NAC was determined using the receiver operating curve. The chosen cut-off was then used to predict HDM driven AR among those with positive systemic test.

Results: 118 patients (29.42 ± 9.32 years, 61.9% female) were included. Nasal spIgE was predictive of positive NAC (AUC 0.93, 95%CI: 0.88-0.98, $p < 0.01$). Among those with positive systemic test, the cut-off value of >0.14 kUA/L was able to predict HDM AR from incidental HDM sensitization with 92% sensitivity and 86% specificity.

Conclusion: Nasal spIgE is comparable to NAC. A cut-off value of >0.14 kUA/L identifies HDM-driven AR from incidental sensitization among patients with positive systemic tests for allergy.

Key words: allergic rhinitis, non allergic rhinitis, local allergic rhinitis, house dust mite, nasal brushings, nasal allergen challenge, nasal specific IgE

Citation:

Hamizan, A. W., Alvarado, R., Arifin, K. T., Zahedi, F. D., Sian, N. C., Jumaat, A. F., Husain, S., Harvey, R. Mucosal brushings for nasal specific IgE to predict house dust mite driven allergic rhinitis. *Asian Pac J Allergy Immunol.* <https://doi.org/10.12932/ap-031122-1495>

Corresponding author:

Aneeza W Hamizan
9th floor, Department of Otorhinolaryngology, HCTM,
Universiti Kebangsaan Malaysia Medical Center,
Jalan Yaakob Latiff, Bandar Tun Razak, 56000, Cheras,
Kuala Lumpur, Malaysia
E-mail: draneeza@gmail.com

Affiliations:

¹ Department of Otorhinolaryngology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

² Rhinology and Skull Base Research Group, St Vincent's Centre for Applied Medical Research, University of New South Wales, Sydney, Australia

³ Department of Biochemistry, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

⁴ Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia

Introduction

House dust mites (HDM), most importantly *Dermatophagoides pteronyssinus* (DP), *Dermatophagoides farina* (DF) are the most common allergens associated with allergic rhinitis (AR) in tropical climates.¹ Skin prick test (SPT) and serum-specific immunoglobulin E (serum spIgE) are the primary diagnostic tools for allergic rhinitis. These techniques identify the HDM specific Immunoglobulin E

(spIgE) distant to the site of pathology. Thus, inconsistencies can occur, with positive systemic test not always correlating with the patient manifesting HDM-driven allergic rhinitis. This is known as incidental sensitization² where the actual cause of nasal symptoms are due to non-allergic pathology. Patients with negative systemic tests are deemed to have nonallergic rhinitis (NAR) but this does not account for the presence of entopy or local allergic rhinitis (LAR).³

The gold standard test to determine HDM driven AR is the nasal allergen challenge (NAC). In this local test, HDM allergens are applied directly onto the nasal cavity and the nasal reactivity is recorded. However, NAC is time-consuming, requires more expensive equipment and training and NAC has subsequently been primarily a research tool. Nasal brushings using a cytology brush is a method used to sample the nasal mucosa for the detection of allergen specific IgE (Nasal spIgE). The head of the inferior turbinate's and anterior septum is brushed after a local anesthetic spray. The procedure is quick and mucosal samples are easily obtained with minimal patient co-operation. Previous studies has proposed mucosal brushings as an alternative local assessment technique^{4,5} but its diagnostic performance compared to NAC needs further validation. The objective of this study was to evaluate the diagnostic performance and determine the cutoff value of nasal spIgE compared to NAC. The usefulness of nasal spIgE to identify HDM driven AR from incidental sensitization among those with a positive systemic test was also assessed.

Methods

This cross-sectional diagnostic study was conducted at a tertiary hospital otorhinolaryngology clinic. Appropriate ethics approval was obtained for this study from the appropriate ethics committee (JEP-2019-792) and study participants provided informed consent.

Study population

Adults (>18 years old) with at least two symptoms of rhinitis (either nose block, sneezing rhinorrhea, or itchy nose) triggered by HDM exposure were consecutively recruited. Pregnant women, patients on prior immunotherapy, prior turbinate surgery, history of anaphylaxis, poorly controlled bronchial asthma and systemic conditions known to affect the nasal mucosa such as primary immunodeficiency and granulomatous diseases were excluded. Patients on intranasal corticosteroids within 1 month before recruitment were also excluded. All patients completed a proforma to assess for nasal symptoms (duration [years], type [intermittent/persistent]), allergic co-morbidities (asthma, eczema, allergic conjunctivitis, family history of atopy) and overall severity of nasal symptoms for the past 1 month using a visual analogue scale (VAS, 0-100 mm). Patients were subjected to both systemic tests for allergy (serum spIgE and SPT) and nasal brushings at the first visit. Patients were then scheduled for NAC at the next available date (within 1 year) to allow mucosal recovery after nasal brushing under local anesthetic and decongestant spray.

Systemic tests for allergy

Serum samples were analysed using an automated immunoassay (ImmunoCAP®, Phadia 100, Thermo Fisher Scientific, Massachusetts, United States) and tested for DP and DF (D1 and D2 respectively). A concentration of ≥ 0.35 kUA/L was defined as positive.

Patients also underwent SPT for HDM (DP and DF) as well as the standard panel of other aeroallergens (cockroach, cat fur, grass (Timothy, Meadow, Rye, Sweet vernal, Cocksfoot, Bermuda), mould (*Aspergillus* sp. Mix, *Alternaria alternata*, *Penicillium*, *Cladosporium herbarum*). Allergens in a 50% glycerine solutions were applied to the volar forearm with a metal lancet, positive and negative control (phenolated glycerol-saline). A wheal of 3 mm or more for allergen and positive control where there was no reaction in the negative control was defined as positive. Patients were defined to have a positive systemic test for HDM when there was either a positive serum spIgE or SPT towards DP or DF.

Nasal specific IgE

The methods for sampling nasal spIgE followed the previous protocol⁶ except it was performed under local anesthesia in an upright position. Both nasal cavities were decongested and anesthetized with 200 μ l Co-Phenylcaine (20 mg lidocaine + 2 mg phenylephrine) topical spray. The cytology brush (Citotest®, Citotest labware manufacturing co., China) was passed between inferior turbinate and septum on the medial edge inferior turbinate head and brushed 5 times for both nostril. The brush head was then cut into a screw cap tube containing 1.5 mL of physiological solution and immediately placed on ice. The suspended cytology brushes were stored at -70°C until processed as previously described.⁶ Briefly, after thawing, suspensions were sonicated to allow cell lysis (Q55 ultrasonicator, at 30% amplitude for 2 minutes at 10-second intervals (10 seconds on, 10 seconds off), and cell debris removed by centrifugation (1690 g, 10 min, 4°C). The cytology supernatants from brushing samples were analysed using the same automated immunoassay as the serum for DP (D1) and DF (D2) which reported values from 0.01 kUA/L to 100 kUA/L. The nasal brushing value was reported both separately as individual allergens DP or DF, or HDM (the highest value for either DP or DF).

Nasal allergen challenge

Patients were advised to stop local or systemic antihistamines and decongestant 7 days prior to scheduled appointment. NACs were performed to test for nasal reactivity towards HDM using an HDM mix in glycerin solution (DP, DF mix, Lofarma, Italy, 100 DBU/ml). Negative control (phenolated glycerol-saline, Lofarma, Italy) was used to evaluate and rule out nonspecific nasal hyperreactivity which could lead to false positive NACs towards HDM. The standardized HDM mix and negative control were diluted in 0.9% normal saline (1:10 solution) and sprayed into both nasal cavities using a metered-dose spray (0.1 ml per spray, 1 puff per nostril). Nasal reactivity towards HDM was assessed objectively by measuring

nasal peak inspiratory flow (NPIF) and nasal airway resistance. NPIF was measured using the NPIF meter (GM Instruments, UK) and nasal airway resistance was measured with four-phase active anterior rhinometry using an NR6 rhinomanometer (GM Instruments, UK) following previously reported techniques.^{7,8} Nasal response was also subjectively scored using the patient reported visual analog score (VAS) for overall symptoms, runny nose, itch, nasal blockage, and sneezing. Both objective and patient reported measures were taken at baseline, 15 minutes after negative control administration, and 15 minutes after HDM mix administration. Patients with non-specific nasal hyperreactivity (defined as increase of $\geq 20\%$ increase in airflow resistance by four-phase active anterior rhinomanometry or flow decrease $\geq 20\%$ in NPIF 15 minutes post negative control administration) were excluded. These patient were excluded as presence of nasal hyperactivity may lead to a false positive NAC. A positive challenge is defined as either : i. a moderate change in both subjective and objective parameters (increase ≥ 23 mm in VAS for any nasal symptoms AND $\geq 20\%$ increase in airflow resistance by four-phase active anterior rhinomanometry or flow decrease $\geq 20\%$ in NPIF) OR ii. A clear change in either the subjective or objective parameters (increase ≥ 55 mm on VAS for any nasal symptoms OR $\geq 40\%$ increase in nasal airway resistance measured by four-phase active anterior rhinomanometry OR $\geq 40\%$ flow decrease in NPIF). (EAACI 2018, NAC Guideline).⁹ All NACs were performed within one year of recruitment.

Rhinitis group definitions

Patients were defined into four rhinitis groups based on a combination of their systemic allergy test (serum spIgE and/or SPT) and NAC towards HDM. Patients with both positive systemic test AND NAC were grouped as HDM-driven AR. Patients with both negative systemic test AND NAC were defined to have NAR. Patients with positive systemic test but negative NAC were grouped as incidental HDM sensitization while patients with the negative systemic test but positive NAC were defined to have LAR. The flow of study is depicted in **Figure 1**.

Statistical Analysis

All statistics and graphic representations of data were performed using SPSS version 25 (IBM Corp., Armonk, NY). Nasal spIgE values were presented as mean \pm standard deviation (SD) for DP, DE, and HDM (using the higher value between the two allergens) in kUA/L. These values were compared between positive and negative NAC results using the T-test. The nasal spIgE was also compared between the rhinitis groups and between the NAC positive criteria subgroup using the one way analyses of variance with a Bonferroni post hoc analysis. Receiver operating curves (ROC) were used to determine the cut-off value (with highest Youden index) for the nasal spIgE to predict a positive NAC. The sensitivity, specificity, likelihood ratio positive (LR+), positive predictive value (PPV), diagnostic accuracy (DA), diagnostic odds ratio (DOR) and diagnostic accuracy (DA) were calculated using the chosen cutoff value. This was similarly done to predict HDM-driven AR among patients with positive systemic allergy.

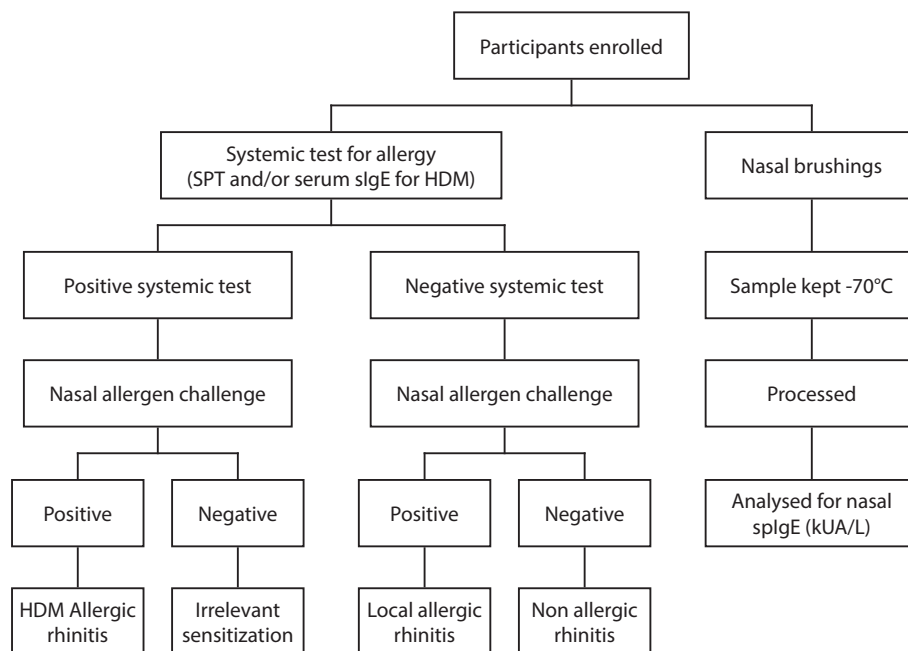


Figure 1. The study flow diagram. Participants who fulfilled the inclusion and exclusion criteria were enrolled and underwent skin prick test (SPT), serum specific Immunoglobulin assay (Serum sIgE) and nasal brushings to test for house dust mite (HDM) allergens. They were then scheduled to undergo nasal allergen challenge and grouped into either HDM allergic rhinitis, irrelevant sensitization, non-allergic rhinitis or local allergic rhinitis.

Results

A total of 121 patients were recruited and all underwent NAC. There were three patients (2.5%) who had non-specific nasal hyperreactivity and were excluded. Among the 118 included patients (29.42 ± 9.32 years old, 61.9% female), 52.7% had persistent rhinitis, 20.3% had eczema, 22% had asthma, 36.4% had allergic conjunctivitis and 72.9% had a family history of atopy. The mean overall VAS was 52.44 ± 25.94 mm.

There were 81.6% with positive SPT, 76.3% with positive serum spIgE and 82.2% with positive systemic test (either SPT or serum spIgE) for HDM. There were 37.7% sensitized to cockroach, 15.8% for cat fur, 4.4% for grass and 4.4% for mould. Overall 36.9% were monosensitized to HDM group only, 44.7% were polysensitized, 16.7% were negative SPT overall while 1.7% were sensitized to other allergens only.

The mean value for nasal spIgE for DP was 1.42 ± 2.07 kUA/L, DF was 1.22 ± 1.77 kUA/L and HDM was 1.51 ± 2.15 kUA/L. There were 78% with positive NAC towards HDM mix. When further divided into rhinitis groups, there were 76% with HDM-driven AR, 6% with incidental HDM sensitization, 16% with NAR, and 2% with LAR.

Associations between Nasal spIgE and NAC

Patients with positive NAC had higher nasal spIgE concentration for DP, DF and HDM compared to those with negative NAC (DP: 1.83 ± 2.37 v 0.15 ± 0.15 kUA/L, $P < 0.01$, DF: 1.54 ± 1.89 v 0.13 ± 0.11 kUA/L, $p < 0.01$, HDM: 1.90 ± 2.41 v 0.15 ± 0.13 kUA/L, $P < 0.01$) (Figure 2).

Associations between nasal spIgE and rhinitis groups

The nasal spIgE concentration were higher among the HDM driven AR group compared to incidental sensitization, NAR and LAR.

1. DP (1.82 ± 2.23 v 0.20 ± 0.25 v 0.12 ± 0.02 v 0.14 ± 0.01 kUA/L, $p < 0.01$).
2. DF (1.57 ± 1.90 v 0.18 ± 0.20 v 0.11 ± 0.02 v 0.13 ± 0.01 kUA/L, $p < 0.01$).
3. HDM (1.94 ± 2.30 v 0.20 ± 0.25 v 0.12 ± 0.02 v 0.14 ± 0.01 kUA/L, $p < 0.01$).

Diagnostic accuracy of nasal spIgE compared to NAC

The nasal spIgE for DP, DF, and HDM gave equivalent performance to predict positive HDM NAC (AUC 0.93, 95%CI: 0.88-0.98, $p < 0.01$) (Figure 3).

A HDM nasal spIgE of >0.14 kUA/L was selected as the positive cut-off which gave the best balance between sensitivity and specificity to predict positive NAC for HDM (Youden index of 0.80). The diagnostic accuracy of HDM nasal spIgE (>0.14 kUA/L) to predict positive NAC was calculated using the 2×2 table (Table 1).

This gave a sensitivity of 91.3%, specificity of 88.5%, PPV of 96.5%, NPV of 74.2%. LR+ 7.9, LR- 0.10, DOR of 79.1 and DA of 90.7% to predict a positive NAC.

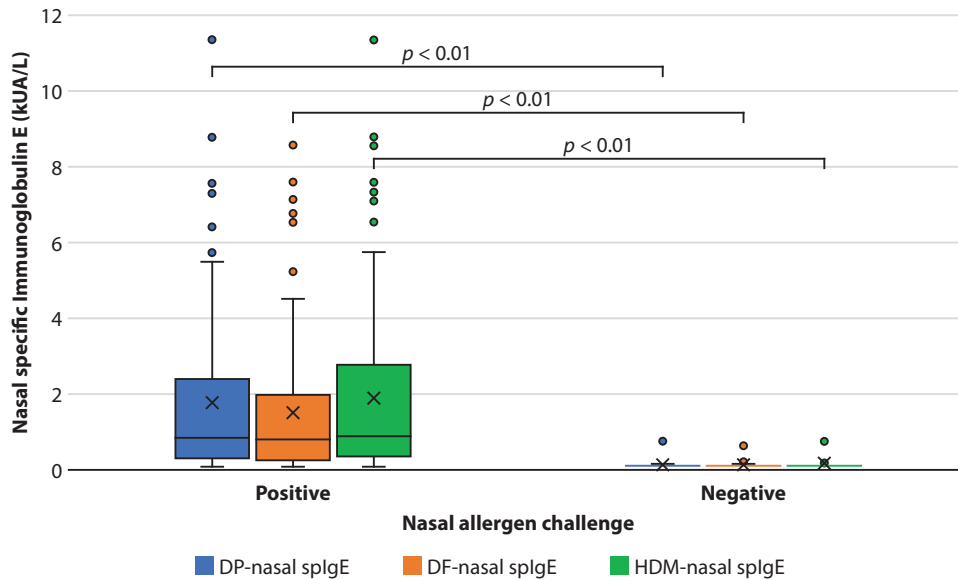


Figure 2. Comparison of nasal house dust mite specific Immunoglobulin E between positive and negative nasal allergen challenges. Participants were assessed for local reactivity to house dust mite (HDM) mix using nasal allergen challenge (NAC) and concentration of nasal specific Immunoglobulin E (nasal spIgE) for each dust mite allergen *Dermatophagoides pteronyssinus* (DP-nasal spIgE) and *Dermatophagoides farina* (DF-nasal spIgE). HDM-nasal spIgE denotes the highest concentration of nasal spIgE between the two individual allergens. Data was represented as mean nasal spIgE concentration \pm standard deviation.

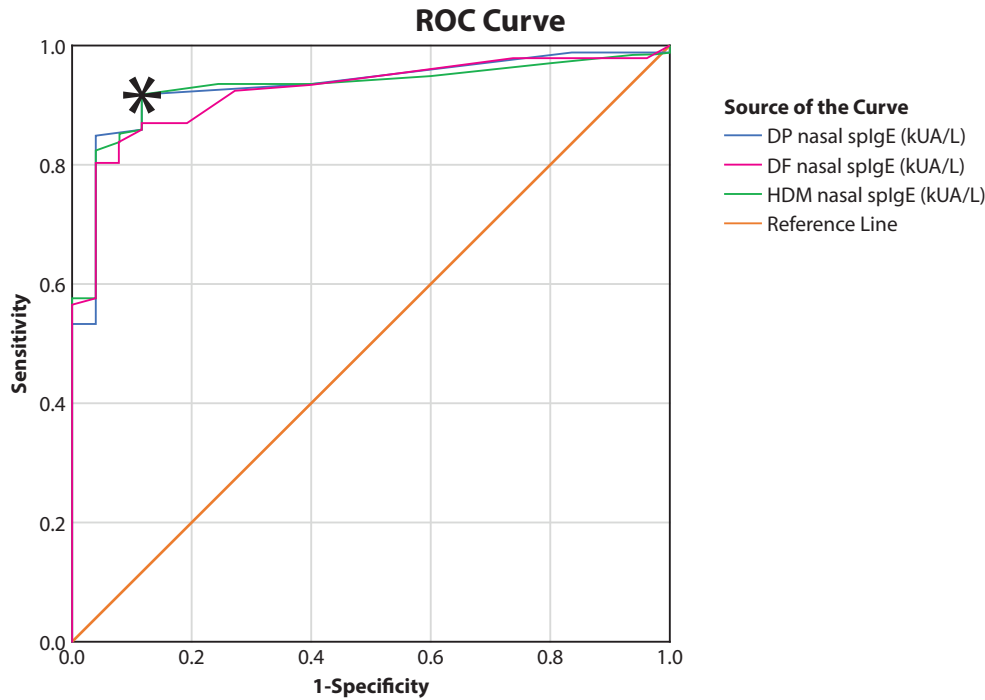


Figure 3. Nasal specific immunoglobulin E house dust mite receiver operating curve (ROC). This ROC depicts the comparison for nasal brushing specific immunoglobulin E (Nasal spIgE) for *Dermatophagoides pteronyssinus* (DP-nasal spIgE) and *Dermatophagoides farinae* (DF-nasal spIgE) and house dust mite (HDM-nasal spIgE) (the highest concentration of nasal spIgE between the two individual allergens) compared to a nasal allergen challenge. The selected cut-off (>0.14 kUA/L) is depicted by the asterisk*.

Table 1. Contingency 2 × 2 table comparing positive nasal specific Immunoglobulin E and nasal allergen challenge.

HDM Nasal specific IgE	NAC		Total
	Positive	Negative	
Positive (> 0.14 kUA/L)	84	3	87
Negative (≤ 0.14 kUA/L)	8	23	31
Total	92	26	118

Abbreviation: HDM, House dust mite; IgE, Immunoglobulin E; NAC, nasal allergen challenge;

Diagnostic accuracy of nasal spIgE to predict HDM driven AR among the positive systemic test.

Among 97 patients with a positive systemic test for HDM, the diagnostic accuracy of nasal spIgE to predict dust mite-driven AR was calculated using the 2 × 2 table (Table 2). This gave a Sensitivity of 92.2%, Specificity 85.7%, PPV 98.8%, NPV 46.2%, LR+ of 6.44, LR- 0.09, DOR of 71.5 and DA of 92.96%.

Table 2. A 2 by 2 contingency table comparing positive house dust mite nasal specific Immunoglobulin E and nasal allergen challenge among patients with the positive systemic test for allergy.

HDM-nasal spIgE	HDM driven AR	Incidental HDM sensitization	Total
Positive (> 0.14 kUA/L)	83	1	84
Negative (≤ 0.14 kUA/L)	7	6	13
Total	90	7	97

Abbreviation: AR, Allergic rhinitis; HDM, House dust mite; NAC, nasal allergen challenge; SpIgE, specific Immunoglobulin E;

Positive nasal specific IgE between rhinitis groups

Patients with HDM-driven AR had a higher rate of HDM nasal spIgE positivity (>0.14 kUA/L) compared to those with incidental dust mite sensitization, NAR and LAR (92% vs 14% vs 11% vs 50%, $p < 0.01$) (Figure 4).

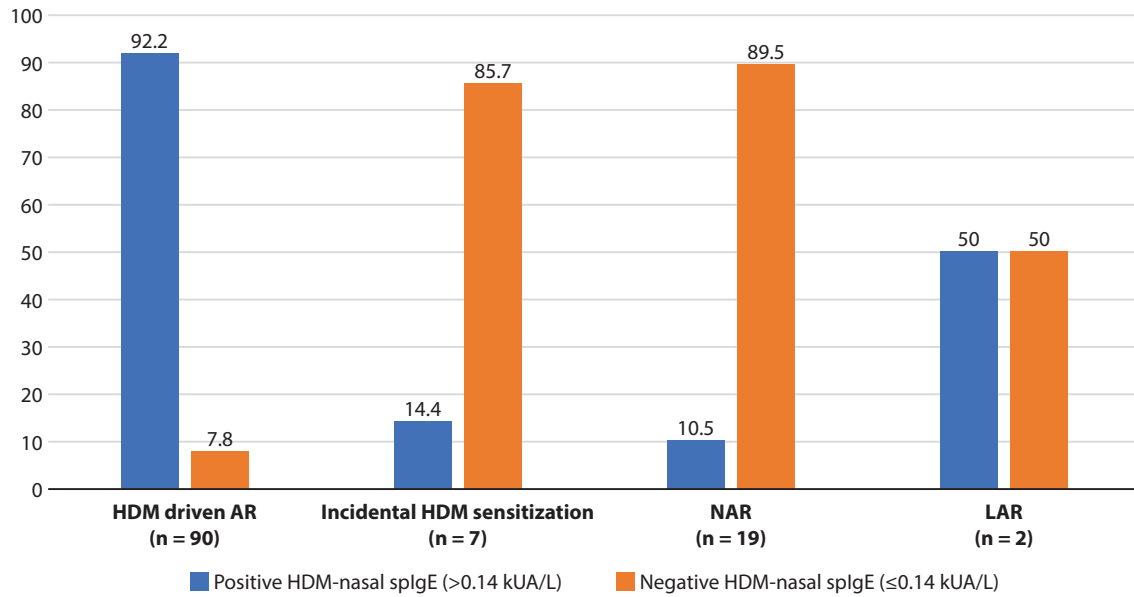


Figure 4. The proportion of patients with positive and negative house dust mite nasal specific IgE (HDM-nasal spIgE) between the rhinitis groups. The rhinitis groups were based on a combination of systemic tests for allergy and nasal allergen challenge (NAC) towards house dust mite (HDM). The HDM driven allergic rhinitis (HDM driven AR) group had both positive systemic test and NAC. The incidental HDM sensitization group had positive systemic test for allergy but negative NAC. The non allergic rhinitis group (NAR) had both negative systemic test and NAC while the local allergic rhinitis (LAR) patient had negative systemic test but positive NAC.

Table 3. The relationship between nasal spIgE and the nasal allergen challenge subgroups. Moderate positive nasal allergen challenge is defined as a moderate change in both subjective and objective parameters. Clear change NAC is defined as a clear change in either the subjective or objective parameters.

	Negative NAC	Moderate change NAC	Clear change NAC	P value
n	26	5	87	
HDM nasal specific IgE (mean ± SD)	0.15 ± 0.13*	0.76 ± 1.01	1.97 ± 2.33	< 0.01
Positive HDM nasal specific IgE (>0.14 kUA/L)	12	80	92	< 0.01
Negative HDM nasal specific IgE (≤0.14 kUA/L)	88.5	20	8	

Abbreviation: HDM, House dust mite; IgE, Immunoglobulin E; NAC, nasal allergen challenge; *significant difference between negative and clear change.

Nasal specific IgE between the nasal allergen challenge positive criteria.

The level of nasal specific IgE was lower in the negative NAC group but there was no difference between the negative NAC and moderate change and no difference between moderate change and clear change NAC group. There were also higher proportion of patients positive nasal spIgE in the moderate and clear change group compared to negative NAC (Table 3).

Discussion

Nasal brushing is one of the many available sampling technique to sample for nasal spIgE. Other methods are blowing out secretion, nasal lavage or insertion of sponge/cotton to absorb secretions. Nasal brushing offer the advantage over these other methods whereby it requires minimal patient co-operation, does not depend on adequate nasal secretions to be blown out, no risk of drenching the patients clothing unlike nasal lavage and is quick without waiting time unlike the absorbed secretion method. This method requires a cytology brush and a screwcap vial containing physiological solution to be available but these are easily found. The nasal brushing suspension can be placed in a freezer in the clinic and stored at minus 70°C for a year before being processed. Sample processing is similar to serum samples except that these samples are sonicated for 2 minutes and requires a refrigerated centrifuge which adds a few minutes of processing time.

Nasal specific IgE has been proposed as an alternative method to assess for allergy at the site of the pathology itself. Reisacher⁵ described the use of mucosal brush technique to detect nasal spIgE among patients with allergic rhinitis and showed its potential to be used as a diagnostic method. Further studies also concluded that nasal spIgE correlated well with systemic tests as well as tissue specific IgE.⁴ Ahn et al.¹⁰ reported that nasal spIgE for HDM was 85-89% sensitive and 92-100% specific but this was using SPT as the gold standard. In this study, the nasal spIgE concentration was higher in those with positive NAC compared to negative NAC. Therefore, nasal spIgE corresponds well with NAC. The good agreement between nasal spIgE and NAC was also previously reported by Fuiano et al.¹¹ In this study children with seasonal *Alternaria* allergy were more likely to positive NAC if there were positive nasal test compared to positive SPT (69% vs 27%). The HDM nasal specific IgE values was also highest in the HDM driven AR compared to incidental sensitization, NAR and LAR group. The NAR group had the lowest concentration indicating that nasal spIgE is also able to detect those who's symptoms are truly not driven by HDM allergy. The ROC was applied to identify a cutoff value for the nasal spIgE with the best balance of sensitivity and specificity to predict a positive NAC. Nasal spIgE correlated well with NAC and a value of >0.14 kU/L is able to predict nasal reactivity towards HDM with high sensitivity and specificity. This cutoff value is similar to other reported cutoff values in the literature which compared local nasal spIgE with either systemic or other local tests.¹²⁻¹⁴

When assessing the nasal spIgE among those with positive systemic sensitization only, it was also sensitive and specific to differentiate patients with true HDM driven AR and incidental sensitization. The nasal spIgE was positive in 92% of HDM driven AR and this was negative in 86% of those with incidental HDM which showed good accuracy. Similarly, Fuiano et al.¹⁵ also showed that among 192 atopic patients, nasal specific IgE was present among 77.5% who had nasal allergy symptoms while it was absent in 86.4% of asymptomatic patients indicating that presence of nasal specific IgE is more clinically relevant than systemic sensitization. In theory, all HDM driven AR should have positive nasal spIgE but there were 7 patients without detectable nasal spIgE (Table 2). This limited sensitivity of nasal spIgE is still not well understood. Another study also found only 23 over 30 patients with HDM AR proven by SPT and positive NAC had positive nasal specific IgE.¹⁶ In conventional systemic allergy, specific IgE are produced in the circulation.¹⁷ There may be less local synthesis and less abundant mucosal spIgE at the time of sampling. Nasal spIgE will also increase after nasal allergen challenge¹⁸ and with seasonal exacerbation¹⁹ indicating its quantity in the nasal mucosa may change but these needs further studies.

In this study, the nasal spIgE was 85% specific to predict HDM driven AR among those with positive systemic tests. However, another similar study reported poor specificity with positive nasal spIgE among 85% of patients with DP driven AR but also positive in 80% of patients with incidental DP sensitization.²⁰ This study sampled the nasal mucosa after the NAC that may lead to increased concentration of nasal spIgE²¹

and may explain the discrepant findings. In this current study, the nasal brushing was performed in clinic and NAC scheduled at a later date similar to how this test will be utilized in a clinical practice. This study faced challenges during the lockdown periods due to COVID 19 pandemic. Hence patients had to reschedule their NAC appointments. Nevertheless, all participants underwent NAC within 1 year of recruitment.

The diagnostic accuracy for the group with negative systemic test was not calculated due to the small number of patients in this group and there was only 2 patients identified to have LAR. Among this non-atopic group, nasal spIgE was negative in 90% of the NAR group but was also negative in 50% of the LAR patients. This is because nasal spIgE tends to correlate with serum specific IgE and larger studies among rhinitis with negative systemic sensitization are needed to further validate this test to identify LAR. El Badawy et al.²² previously reported nasal specific IgE was present (>0.35 IU/ml) in more than half of the LAR population with mean value of 10.9 ± 1.7 kUA/L for DP indicating nasal spIgE as a promising tool to screen for LAR. However this was disputed by another study which reported only 3 out of 7 patients with LAR had positive nasal specific IgE (>0.12 kUA/L) for DP post nasal challenge with poor sensitivity (48%) and specificity (50%).²⁰ Another study which compared LAR with healthy control reported that nasal specific IgE (>0.14 kUA/L) was able to discriminate LAR from healthy non atopic with 100% specificity and 100% PPV with fair test performance (AUC 0.67).¹² The role of nasal spIgE to differentiate LAR from NAR may need further larger studies. The lack of LAR patients in this study suggests that LAR is less prevalent for HDM in the tropical region. Previous studies have found that LAR is less prevalent for HDM allergen compared to pollen²³ and is also less prevalent in the Asian region.²⁴ A recent study also did not find any LAR among non-atopic rhinitis.²⁵

In this population 6% were found to have irrelevant sensitization towards HDM. Interestingly, 3 out of these 7 patients had positive skin prick test but with negative serum sIgE. Prior studies have shown that a stronger wheal reactions have higher likelihood of positive nasal allergen challenge and this may have contributed to the false positive results.^{26,27}

The positivity criteria for NAC in this study was based on the EAACI position paper standardization.⁹ The majority of patients (87/92) with positive NAC exhibited clear changes in either subjective or objective measures. The nasal spIgE levels were higher in the clear positive group compared to negative NAC but there was no statistical difference between the moderate change group and negative NAC. This is likely due to the lack of patients with moderate changes and may need further studies.

Nasal brushings could be a useful test to confirm nasal symptoms truly driven by allergy among those with systemic sensitization. This is because nasal spIgE is comparable to NAC and accurately identified HDM driven AR from rhinitis with incidental HDM sensitization. Nasal brushings for spIgE is also a quick and accurate test to assess for allergen relevance which is easy to perform and saves time compared to other local sampling method for spIgE.

Conclusion

Nasal spIgE is able to predict HDM driven AR confirmed by NAC. A cut-off value of >0.14 kUA/L identifies HDM-driven AR from incidental sensitization among patients with positive systemic tests for allergy. This test may be a useful alternative to assess for nasal allergy.

Acknowledgement

The authors would like to thank Dr. Tan Jen Kit, Siti Nor Rodhiah Rosaidee and the department of biochemistry for the laboratory support.

Conflict of interest

Richard J Harvey is consultant with Medtronic, Stryker, Novartis, Meda, GSK, Sanofi and NeilMed pharmaceuticals. Research grant funding received from Glaxo-Smith-Kline. He has been on the speakers' bureau for Astrazeneca, Glaxo-Smith-Kline, Meda Pharmaceuticals and Seqirus. All other authors have no financial disclosures or conflicts of interest.

Funding

This study was funded by Dana Universiti penyelidikan, Ministry of education, Malaysia (GGPM-2019-049)

Author contributions

- Aneeza Hamizan was involved in acquisition of data, lab work, data analyses and wrote the first draft of the article.
- Raquel Alvarado was involved in the conception and design of the study, data analyses and revised the article critically for important intellectual content.
- Khaizurin Tajul was involved in conception and design and lab work.
- Farah Dayana and Salina Husain were involved with conception and design of this study and revised it critically for important intellectual content.
- Anna Fariza and Ng Chong Sian were involved in acquisition of data and data analyses.
- Richard Harvey made substantial contributions to conception and design of study, acquisition and interpretation of data and revised the article critically for important intellectual content.
- All authors gave final approval of the version to be published.

References

1. Zahedi FD, Gendeh BS, Husain S. Sensitisation to common allergens in children with allergic rhinitis. *Brunei Int Med J.* 2011;7:200-6.
2. Bodtger U. Prognostic value of asymptomatic skin sensitization to aeroallergens. *Curr Opin Allergy Clin Immunol.* 2004;4:5-10.
3. Campo P, Salas M, Blanca-López N, Rondón C. Local allergic rhinitis. *Immunol Allergy Clin.* 2016;36:321-32.
4. Hamizan A, Alvarado R, Rimmer J, Sewell WA, Barham HP, Kalish L, et al., editors. Nasal mucosal brushing as a diagnostic method for allergic rhinitis. *Allergy Asthma Proc.* 2019;40:167-72.
5. 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.

6. Saricilar EC, Hamizan A, Alvarado R, Rimmer J, Sewell W, Tattersall J, et al. Optimizing protein harvest from nasal brushings for determining local allergy responses. *Am J Rhinol Allergy.* 2018;32:244-51.
7. Mo S, Gupta SS, Stroud A, Strazdins E, Hamizan AW, Rimmer J, et al. Nasal Peak Inspiratory Flow in Healthy and Obstructed Patients: Systematic Review and Meta-Analysis. *The Laryngoscope.* 2021;131:260-7.
8. Barham HP, Knisely A, Christensen J, Sacks R, Marcells GN, Harvey RJ. Costal cartilage lateral crural strut graft vs cephalic crural turn-in for correction of external valve dysfunction. *JAMA Facial Plast Surg.* 2015;17:340-5.
9. Augé J, Vent J, Agache I, Airaksinen L, Campo Mozo P, Chaker A, et al. EAACI Position paper on the standardization of nasal allergen challenges. *Allergy.* 2018;73:1597-608.
10. Ahn JY, Hong SJ, Choi BS. Clinical evaluation of techniques for measuring nasal-specific immunoglobulin E in pediatric patients. *J Korean Med. Sci.* 2017;32:2005-8.
11. Fuiano N, Fusilli S, Incorvaia C. A role for measurement of nasal IgE antibodies in diagnosis of Alternaria-induced rhinitis in children. *Allergol. Immunopathol.* 2012;40:71-4.
12. Campo P, del Carmen Plaza-Seron M, Eguiluz-Gracia I, Verge J, Galindo L, Barrionuevo E, et al., editors. Direct intranasal application of the solid phase of ImmunoCAP® increases nasal specific immunoglobulin E detection in local allergic rhinitis patients. *Int Forum of Allergy Rhinol.* 2017;8:15-9.
13. Gelardi M, Guglielmi AV, Iannuzzi L, Quaranta VN, Quaranta N, Landi M, et al. Local allergic rhinitis: entopy or spontaneous response? *World Allergy Organ J.* 2016;9:1-6.
14. Hamizan AW, Rimmer J, Alvarado R, Sewell WA, Tattersall J, Barham HP, et al. Turbinate-specific IgE in normal and rhinitic patients. *Am J Rhinol Allergy.* 2019;33:178-83.
15. Fuiano N, Fusilli S, Passalacqua G, Incorvaia C. 10 Allergen-specific immunoglobulin E in the skin and nasal mucosa of symptomatic and asymptomatic children sensitized to aeroallergens. *J Investig Allergol Clin Immunol.* 2010;20:425.
16. Rondón C, Romero JJ, López S, Antúnez C, Martín-Casañez E, Torres MJ, et al. Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. *J Allergy Clin Immunol.* 2007;119:899-905.
17. Powe D, Bonnin A, Jones N. 'Entopy': local allergy paradigm. *Clin Exp Allergy.* 2010;40:987-97.
18. Rondón C, Fernández J, López S, Campo P, Doña I, Torres MJ, et al. Nasal inflammatory mediators and specific IgE production after nasal challenge with grass pollen in local allergic rhinitis. *J Allergy Clin Immunol.* 2009;124:1005-11.e1.
19. Naclerio RM, Adkinson Jr NE, Moylan B, Baroody FM, Proud D, Kagey-Sobotka A, et al. Nasal provocation with allergen induces a secondary serum IgE antibody response. *J Allergy Clin Immunol.* 1997;100:505-10.
20. Santamaría L, Calle A, Calvo V, Sánchez J, Cardona R. Nasal specific IgE to Der p is not an acceptable screening test to predict the outcome of the nasal challenge test in patients with non-allergic rhinitis. *World Allergy Organ J.* 2020;13:100461.
21. López S, Rondón C, Torres M, Campo P, Canto G, Fernandez R, et al. Immediate and dual response to nasal challenge with *Dermatophagoides pteronyssinus* in local allergic rhinitis. *Clin Exp Allergy.* 2010;40:1007-14.
22. ELBadawy NE, El-Anwar MW. Assessment of nasal immunoglobulin E level in atopic and non-atopic rhinitis patients: a tool for diagnosis of local allergic rhinitis. *Egypt J Immunol.* 2016;23:45-56.
23. Hamizan AW, Rimmer J, Alvarado R, Sewell WA, Kalish L, Sacks R, et al., editors. Positive allergen reaction in allergic and nonallergic rhinitis: a systematic review. *Int Forum Allergy Rhinol.* 2017;7:868-77.
24. Rondón C, Eguiluz-Gracia I, Campo P. Is the evidence of local allergic rhinitis growing? *Curr Opin Allergy Clin Immunol.* 2018;18:342-9.
25. Eckrich J, Hinkel J, Fischl A, Herrmann E, Holtappels G, Bachert C, et al. Nasal IgE in subjects with allergic and non-allergic rhinitis. *World Allergy Organ J.* 2020;13:100129.
26. Kanthawatana S, Maturim W, Foonan S, Trakultivakorn M. Skin prick reaction and nasal provocation response in diagnosis of nasal allergy to the house dust mite. *Allergy Asthma Immunol.* 1997;79:427-30.
27. Chusakul S, Phannaso C, Sangsarsri S, Aejumjaturapat S, Snidvongs K. House-dust mite nasal provocation: a diagnostic tool in perennial rhinitis. *Am J Rhinol Allergy.* 2010;24:133-6.