

Specific immunoglobulin E in nasal secretions for the diagnosis of local allergic rhinitis*

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Rhinology 57: 4, 313 - 320, 2019
<https://doi.org/10.4193/Rhin18.292>

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***Received for publication:**
 December 2, 2018

Accepted: May 3, 2019

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Abstract

Background: The diagnostic value of serum specific Immunoglobulin E (sIgE) and nasal allergen provocation test (NAPT) has been well investigated in local allergic rhinitis (LAR). We hypothesized that nasal local sIgE could be used for the diagnosis of LAR instead of NAPT.

Methods: This was a prospective single center study. Overall, 212 chronic rhinitis patients were screened, of whom 73 were recruited based on negative findings for serum IgE and positive findings for local eosinophils. Ten healthy subjects were also recruited as controls. All participants completed questionnaires at recruitment to record their demographic data, nasal symptom severity, and physician-diagnosed comorbid asthma. Symptom severity was recorded using a visual analogue scale (VAS) of 10 cm and allergic status was assessed by serum sIgE. Nasal secretions were collected for analysis of local sIgE and eosinophils, and NAPT was performed for confirmation of LAR.

Results: Overall, 14 patients demonstrated positive local sIgE results. Twelve of these patients had significantly higher local sIgE levels compared to controls, and also demonstrated positive NAPT results. The VAS scores, nasal airway resistance measured by active rhinomanometry, and the levels of local sIgE, ECP, histamine and leukotriene C4 were significantly increased from baseline values following NAPT. Sensitivity, specificity, and diagnostic accuracy of local sIgE for diagnosis of LAR were 91.7% respectively.

Conclusions: The measurement of local sIgE levels in nasal secretion is a reliable and effective diagnostic method for LAR.

Keywords: diagnosis, local allergic rhinitis, nasal allergen provocation test, specific immunoglobulin E

Introduction

Rhinitis is defined as an inflammation of the nasal mucosa, usually characterized by rhinorrhea, sneezing, nasal obstructive and itching ⁽¹⁾. Rhinitis is a common respiratory disease, which currently affects about 20–40% of the population in the western countries, and its incidence is still rising ⁽²⁾. The adverse impact of rhinitis has not only been associated with chronic rhinosinusitis, asthma, psychological impairment and sleep impairment, but also with decreased study and work productivity ⁽³⁻⁶⁾. Rhinitis has been traditionally classified as allergic rhinitis (AR) and non-

allergic rhinitis, and the diagnosis has been based on the clinical history, endoscopic examination, skin prick test (SPT) or serum IgE levels to different kinds of sensitizing allergens ⁽¹⁾. However, with increasing focus on optimizing personal treatment in recent years, especially in the field of chronic upper airway diseases, the two broad phenotypes of AR and non-AR cannot meet the needs of precision medical, especially with more and more phenotypes of rhinitis being classified. Huggins and colleagues ⁽⁷⁾ first demonstrated that specific Immunoglobulin E (sIgE) antibodies were produced locally in AR

patients with negative skin tests; and nearly thirty years later, based on similar findings Powe and colleagues⁽⁸⁾ defined this phenomenon as “entopy”. Recently, Rondon and colleagues⁽⁹⁾ have defined this specific phenotype of rhinitis as “local allergic rhinitis” (LAR), which further more recent research has suggested that LAR is an entity well differentiated from AR⁽¹⁰⁾. Rondon and colleagues⁽¹⁰⁻¹²⁾ have further proposed that a diagnosis of LAR may be made based on several criteria; including 1) local production of IgE, 2) Th2 inflammatory pattern in nasal secretion when exposed to sensitizing allergens, and 3) positive results of nasal allergen provocation test (NAPT) without systemic atopy including increased level of sIgE, tryptase and eosinophil cationic protein (ECP) in the nasal secretion. There is little doubt that NAPT is the most important method for the diagnosis of LAR, and that it is potentially important in the proper selection of an individualized therapeutic strategy in clinically complicated cases with sensitizations to various antigens^(9,13-15). However, NAPT also has several limitations in clinical practice; in particular the absence of standardized methods and some reagents, the wide variety of test protocols, need to be performed by trained personnel under close medical supervision and are difficult to perform on pediatric patients^(16,17).

We have recently demonstrated that the level of sIgE levels in nasal secretion (local sIgE) is an effective and reliable alternative to serum IgE for a diagnosis of allergic rhinitis⁽¹⁸⁾. Thus, we have hypothesized that the level of local sIgE may also be effective, relatively simple and reliable alternative to NAPT for the diagnosis of LAR.

Materials and methods

Study design and patients

This prospective study was conducted from 1st February 2017 to 31st August 2017, in a single center. Overall, 212 patients suspected to have rhinitis based on the presence of common symptoms of nasal obstruction, rhinorrhea, sneezing and itching were screened consecutively from the allergy-rhinology clinic of Beijing TongRen Hospital. Questionnaires were completed by each participant to record demographic data and nasal symptom severity; and diagnosis of AR was confirmed based on the presence of symptoms and clinically relevant serum sIgE results. Similarly, physician-diagnosed comorbid asthma was assessed according to presence of symptoms and lung function tests. Nasal secretions were collected for analysis of local sIgE and eosinophils, which were assessed according to the study by Howarth and colleagues⁽¹⁹⁾. Thus, to be included in the study, eligible patients were required to have findings for both negative serum IgE and positive local eosinophils in nasal secretions, and could therefore be classified as LAR or NARES patients. NAPT was performed on these patients; and setting the NAPT results as the golden standard, the value of local sIgE in diagnosing LAR was evaluated.

Patients with any immunological disease, chronic rhinosinusitis and/or nasal polyposis, any respiratory infection in the previous 4 weeks were excluded, as were pregnant and lactating women. CRS patients were excluded based on history, nasal endoscopic examination and, findings from CT scans. Patients were also excluded if they had taken systemic corticosteroids over the past 3 months, intranasal corticosteroids over the past 4 weeks, antihistamines over the past 2 weeks, or vasoconstrictors over the past 1 week. Additionally, based on the diagnostic criteria of LAR, patients found to have positive serum sIgE results and negative local eosinophils results were also excluded from the cohort. The study was conducted in full accordance with Declaration of Helsinki and approved by the Medical Ethics Committee of Beijing TongRen Hospital; and all patients provided written informed consent prior to entry into the study and collection of data.

Visual analogue scale

The severity of nasal symptoms; including nasal obstruction, anterior or posterior rhinorrhea (watery, mucous or purulent), sneezing and nasal/eye itching was recorded using a visual analogue scale (VAS) of 10 cm. Each symptom was categorized as ‘mild’ (VAS: 0–3 cm), ‘moderate’ (VAS: >3–7 cm), or ‘severe’ (VAS > 7 cm).

Rhinomanometry and nasal airway resistance

Nasal airway resistance (NAR) was assessed at a transnasal pressure difference of 150 Pa by active rhinomanometry (ATMOS Medizin Technik GmbH&Co., Feldkirch, Germany).

Serum sIgE

Serum sIgE levels to common aeroallergens were determined using a fluoroenzyme immunosorbent assay (UniCAP, Uppsala, Sweden); with a value for serum sIgE \geq 0.35 kU/L regarded as positive. The sIgE examination was performed with a panel of allergens including *Dermatophagoides farinae* (*Der f*), *Dermatophagoides pteronyssinus* (*Der p*), *Candida albicans*, *Mugwort*, *Penicillium notatum*, *Cladosporium*, *Alternaria*, and *Aspergillus*.

Local sIgE

Local sIgE was determined in nasal secretions, which were collected and processed as described previously⁽²⁰⁾. Briefly, 30 minutes before NAPT and immediately following NAPT when the patient experienced symptoms of irritation, nasal secretions were obtained by inserting a postoperative sinus sponge pack in each nostril for about 5 minutes. The quantity of secretions collected in each sponge was determined by comparing the weight of the sponge before and after insertion into the nasal cavity, and the secretion was extracted from the sponge by addition of 2 mL of 0.9% sodium chloride solution.

All sponges were stored at 4 °C for at least two hours and then transferred to a 5 mL BD syringe. The bulk of the nasal secretion

was forced out of the sponges using the piston of the syringe and centrifuged at 1500 g for 15 minutes at 4 °C. The supernatants were separated and stored in aliquots at –20 °C until analysis for the presence of sIgE. At the time of assay, an aliquot was also assessed to make sure there was no contamination by bacteria or fungi, or disturbance in the other factors. Local sIgE in nasal secretions was assessed using the fluoroenzyme immunosorbent assay (UniCAP, Uppsala, Sweden) and the panel of aeroallergens as for serum. Again a value for sIgE ≥0.35 kU/L was regarded as positive.

Nasal allergen provocation test

Nasal allergen provocation test (NAPT) was performed according to the guidelines of European Academy of Allergy and Clinical Immunology (21). The patients were first seated at room temperature for 30 minutes to minimize the effects of daily-life stimulation, before undergoing saline (0.9% NaCl) challenge tests to exclude nasal hyperreactivity. After a 30-min adaptation period, the patients were challenged with saline, Der-f and mugwort solutions (0.004mg/ml, 0.04 mg/ml, 0.4 mg/ml, and 4mg/ml, WOLWOPHARMA, Zhejiang, China), delivered to the inferior turbinate using a nebulizer with a fixed volume of 100 ul per puff (the better patent side). Solutions were applied to both nostrils in increasing concentrations at 10 minutes intervals; with the subjects holding the breath after a deep inspiration to avoid allergen being inhaled into the lower airways; until the appearance of allergic symptoms. The clinical symptoms and the change in nasal airway resistance (NAR) were reassessed with active rhinomanometry after NAPT.

Total symptom scores represented the sum of the scores for: sneezing (0–2 sneezes = 0; 3–5 = 1; >5 = 2); rhinorrhea (moderate = 1; severe = 2); tearing+itching (eyes and/or throat = 1; conjunctivitis+ cough+urticaria and/or dyspnea = 2) (22). NAPT was considered positive if the total symptom score was ≥4 or nasal airflow was reduced by 60% or more from the baseline level. Challenge was also considered positive if nasal airflow was reduced by 20% or more plus the symptom score was ≥3. To avoid any stimulation of the nasal mucosa caused by postoperative sinus sponge pack in each nostril, the NAPT was performed at least 1h after removing the sponge from the nostril.

Measurement of inflammatory mediators

Inflammatory mediators were measured in nasal secretions collected before and after NAPT, as described above for sIgE. Commercial ELISA kits were used to measure the levels of total protein (Beyotime, Beijing, China); and the levels of eosinophil cationic protein (ECP) (CUSABIO, Wuhan, Hubei province, China), the levels of histamine (CUSABIO), and the levels of leukotriene C4 (R&D Systems, Minneapolis, MN, USA). The level of each mediator was calculated as the concentration in ng/g protein. When the level of a mediator measured was below the detecti-

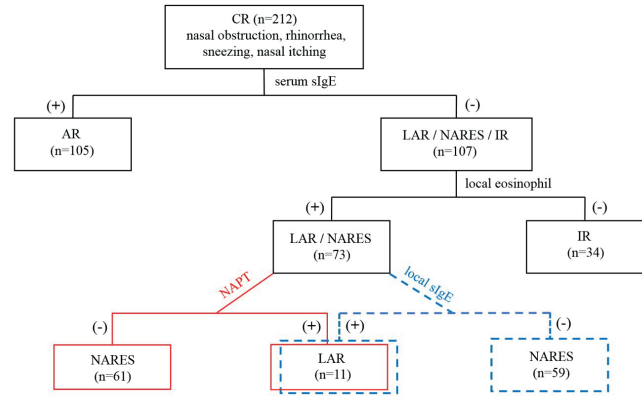


Figure 1. The stages for diagnosis of different chronic rhinitis endotypes. The red line (NAPT) indicates the conventional diagnostic stage (golden standard) and the blue dotted line (local sIgE) indicates the newly proposed diagnostic step differentiation between LAR and NARES. AR, allergic rhinitis; CR, chronic rhinitis; IR, idiopathic rhinitis; LAR, local allergic rhinitis; NAPT, nasal allergen provocation test; NARES, nonallergic rhinitis with eosinophilia syndrome.

on level in the initial measurement, the results of that particular sample was excluded.

Statistical analysis

Setting the NAPT results as the golden standard, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy (DA) of local sIgE were determined for predicting the value of LAR. A true positive value was defined as the ability of local sIgE to accurately predict the diagnosis of LAR, and a true negative value was defined as failing to diagnose LAR. The variables between the clusters were compared by one-way analysis of variance, Chi-square test and Tukey’s test using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 7.0 software (GraphPad Software, Inc., La Jolla, CA, USA). Data were expressed as median and interquartile range, unless otherwise specified. Statistical significance was set at a p-value ≤ 0.05.

Results

Figure 1 shows the stages in the diagnosis of the different endotypes of chronic rhinitis in the present study; with the possibility of replacing NAPT by measurement of local sIgE for differentiating between LAR and NARES. Overall, 212 patients with rhinitis symptoms (nasal obstruction, rhinorrhea, sneezing and nasal itching) were screened and 73 eligible patients (42 males and 31 females; age range 25 years to 54 years, mean = 38.0±12.4 years) were further investigated. Similarly 10 healthy subjects were also investigated as controls. Of the eligible rhinitis patients, 14 had positive local sIgE results and 2 patients concomitant asthma (Table 1). After performing the NAPT on these 73 rhinitis patients, 12 rhinitis patients (7 males and 5 females, mean =

Table 1. Demographic characteristics, NAPT and local sIgE results of patients deemed to have LAR.

No.	Age	Gender	Asthma	NAPT	Local sIgE
1	39	M	N	+	+
2	47	M	N	+	+
3	40	F	N	+	+
4	35	M	Y	+	+
5	30	M	N	+	+
6	37	M	N	+	-
7	35	F	N	+	+
8	53	M	N	-	+
9	45	F	N	+	+
10	30	F	Y	+	+
11	33	M	N	+	+
12	35	M	N	+	+
13	54	F	N	+	+
14	28	M	N	-	+
15	36	F	N	-	+

38.3±17.3 years) were found to show positive results, and were thus diagnosed as LAR (Tables 1 and 2); with 11/12 of these patients were part of the 14 rhinitis patients, and ranged from 30 years to 54 years in age. Thus, 11 patients were diagnosed as LAR by both NAPT and local sIgE (Figure 1). The sensitivity, specificity, PPV, NPV, and DA for local sIgE as a diagnostic tool

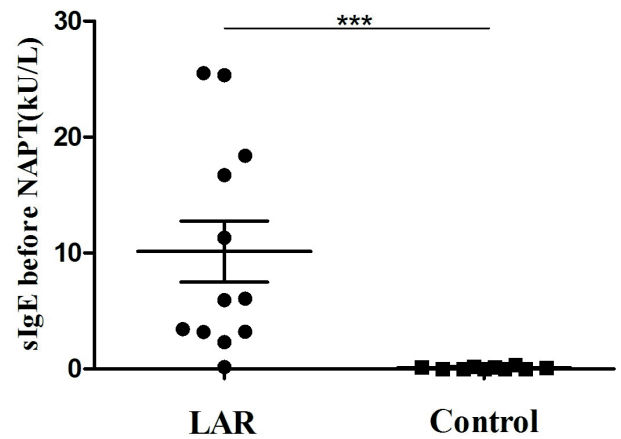


Figure 2. Measurement of specific Immunoglobulin E (sIgE) before nasal allergen provocation test (NAPT).

for the diagnosis of LAR were 91.7% (95% CI, 64.6% to 98.5%), 95.1% (95% CI, 86.5% to 98.3%), 78.6% (95% CI, 52.4% to 92.4%), 98.3% (95% CI, 91.0% to 99.7%), and 94.5% (95% CI, 86.7% to 97.9%), respectively.

To verify the diagnosis of LAR, clinical markers and laboratory biomarkers were also measured following NAPT. Table 2 shows the demographic characteristics, nasal symptoms VAS scores, nasal airway resistance and the level of local sIgE before and after NAPT of patients diagnosed as LAR. The local sIgE level was significantly higher in the LAR group than the healthy control group before NAPT (Figure 2). Among these patients, one patient (number 12; italicized) had a positive NAPT result,

Table 2. The Demographic characteristics and VAS, nasal airway resistance and local sIgE level at baseline and after NAPT of LAR patients.

No.	Age	Gender	Asthma	VAS		NAR		Local sIgE	
				Before	After	Before	After	Before	After
1	38	M	N	20	25	2.203	8.005	11.29	33.72
2	46	M	N	10	30	0.377	2.394	3.21	6.96
3	41	F	N	22	40	0.599	1.184	2.32	5.46
4	34	M	Y	15	25	0.522	5.264	16.75	26.31
5	30	M	N	16	40	0.279	0.960	25.54	30.22
6	36	F	N	14	14	0.806	1.279	5.96	29.51
7	55	F	N	18	40	1.530	6.329	18.41	33.52
8	46	F	N	18	22	0.322	2.021	25.35	25.96
9	31	F	Y	21	27	1.373	2.070	3.22	8.25
10	33	M	N	21	34	0.687	1.264	3.66	9.45
11	35	M	N	15	26	0.733	1.178	6.17	15.31
12	36	<i>M</i>	<i>N</i>	<i>16</i>	<i>25</i>	<i>0.801</i>	<i>1.278</i>	<i>0.17</i>	<i>0.31</i>

N=no; Y=yes; M = male; F = female; VAS = visual analogue scale; Der f= Dermatophagoides farinae; NAPT = nasal allergen provocation test; NAR = nasal airway resistance

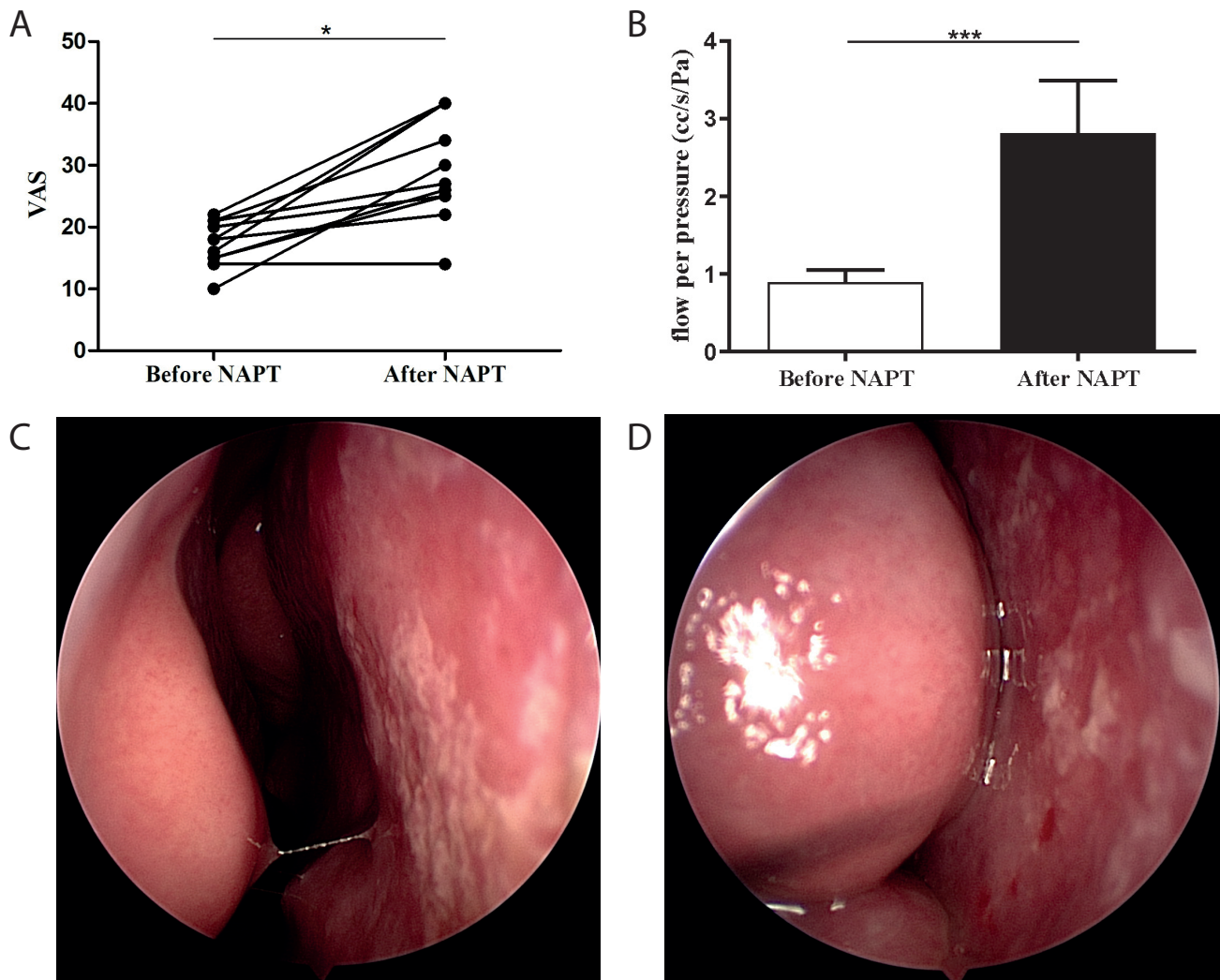


Figure 3. Effect of nasal allergen provocation test (NAPT) in patients with local allergic rhinitis (LAR). NAPT significantly increased the symptom score (A) and nasal airway resistance (NAR) (B); and led swelling of the inferior turbinate and production of large quantities of watery secretions in the nasal cavity (representative endoscopic images of the nasal cavity before (C) and after (D) NAPT).

but a negative local sIgE result. Overall, the VAS scores and NAR in the LAR group were significantly increased from baseline after NAPT (Figures 3A and 3B). The diluent saline solution did not significantly alter the resting NAR (cc/s/Pa) in these patients (before saline=20 vs after saline=20). Endoscopic examination demonstrated that NAPT also increased swelling of the inferior turbinate and watery secretion in the nasal cavity in these patients (Figures 3C and 3D). Similarly, assessment of inflammatory mediators in nasal secretions demonstrated that the levels of local sIgE, ECP, histamine and leukotriene C4 were also significantly increased from baseline after NAPT in LAR patients (Figure 4).

Discussion

Chronic rhinitis continues to be a significant problem that decreases the quality of life of affected individuals ⁽¹⁾. As a specific

phenotype of chronic rhinitis, LAR has been widely discussed in the recent years ^(2,8,9-14). Furthermore, according to the currently employed diagnostic criteria of LAR, many patients previously diagnosed as non-allergic rhinitis patients should be given a diagnosis of LAR ⁽¹²⁾. With the development of NAPT, increasingly more patients have been diagnosed as LAR; with this endotype affecting 25.7% of the rhinitis population and including about half of the patients previously diagnosed with nonallergic rhinitis ⁽¹⁰⁾.

For the diagnosis of LAR, neither skin prick testing nor determination of the presence of serum sIgE antibodies is thought to be useful, and a NAPT is needed to identify the sensitizing allergen or allergens ⁽¹¹⁾. However, NAPT is not available in every clinic, and is also somewhat limited as it is difficult to apply in children and is time consuming ⁽²³⁾. In contrast, nasal secretion is easy to obtain, and contains a variety of inflammatory cells, mediators,

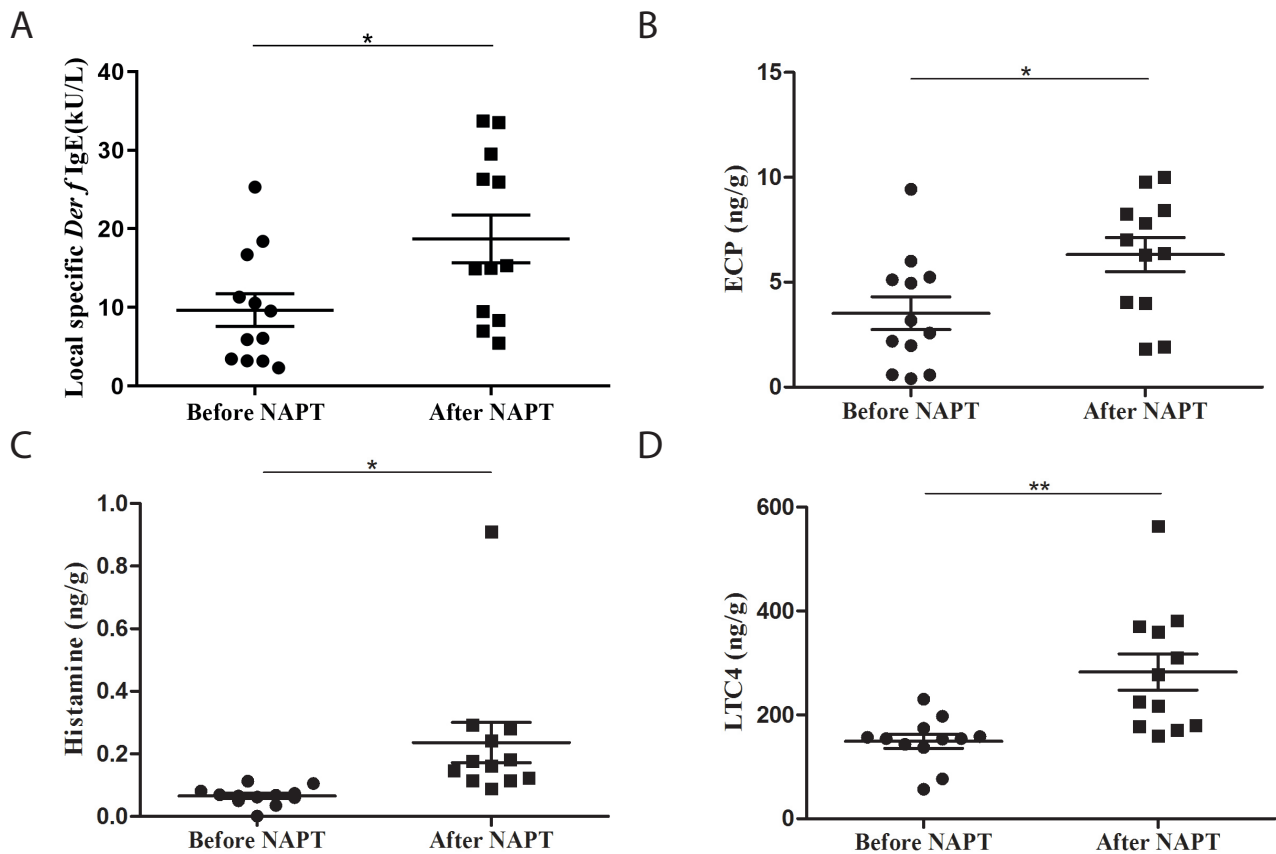


Figure 4. Measurement of *Der f*-specific Immunoglobulin E (*Der f*-sIgE) and inflammatory mediators before and after nasal allergen provocation test (NAPT). A, *Der f*-sIgE; B, eosinophil cationic protein (ECP); C, histamine; D, leukotriene C4 (LTC4).

and other immunologic markers. Several studies have shown that local specific IgE is synthesized in the nasal mucosa of rhinitis patients^(7,8), and findings from a previous study of ours has suggested that nasal secretion could be used for diagnosis of LAR⁽¹⁸⁾. Therefore, for the current study we hypothesized that local sIgE in nasal secretion could be used for the diagnosis of LAR. In this study, only rhinitis patients who had negative serum sIgE results and positive results of local eosinophils were enrolled to rule out any systemic allergic reactions, and the incidence of LAR was verified by the presence of local sIgE and the effect of NAPT with *Dermatophagoides farinae* (*Der f*) and mugwort. Using these diagnostic criteria, our study demonstrated that only around 20% (14/73) of the study cohort comprised LAR patients, of whom the 78.6% (11/14 patients) had positive NAPT results for *Der f*. This result was interesting because none of them was allergic to mugwort. This might be due to these patients were recruited from February to May and mugwort is the main aeroallergen in Autumn in Beijing (duration from late July to end of September)⁽²⁴⁾. One patient demonstrated a positive NAPT reaction, but a negative local sIgE result. Despite the negative result for local sIgE, this patient would be diagnosed as LAR according to the earlier studies⁽¹¹⁻¹⁴⁾. Similarly, two patients who had a positive result for low levels of local sIgE, but negative NAPT results. Based on classification criteria of Rondon and colleagues⁽¹¹⁾,

these two patients could not be diagnosed as LAR, because they did not meet all three requirements of 1) local production of IgE, 2) Th2 inflammatory pattern in nasal secretion when exposed to sensitizing allergens, and 3) positive results of nasal allergen provocation test (NAPT) without systemic atopy, including increased level of sIgE, tryptase and eosinophil cationic protein (ECP) in the nasal secretion. Collectively, these findings indicate that the diagnostic accuracy of local sIgE for LAR was 94.5%. There was an earlier report that local sIgE also could be detected in nonallergic rhinitis patients and healthy subjects at baseline⁽²⁵⁾. In the present study, there were three rhinitis patients had positive sIgE but negative NAPT results (Table 1) and this was in accordance with the former study⁽²⁵⁾. However, none of the healthy control reached diagnostic threshold in our study despite 5 of them had sIgE results lower than 0.35 kU/L (The sIgE results of the rest 6 healthy control were 0). This was might be due to the different diagnostic kits in these two studies. In the current study, all the patients with LAR had a positive rapid response; and none suffered a late response (data not show). These findings are in accordance with those of Rondon and colleagues⁽¹⁵⁾ and support the existence of a persistent local synthesis of sIgE in nasal mucosa of patients with LAR that rapidly enhances after nasal exposure to aeroallergens⁽⁹⁾. Furthermore, ECP has been shown as one of the indicators of LAR⁽¹⁰⁾. In the

present study, we evaluated several mediators, besides ECP, as markers of LAR; and found that the levels of ECP and leukotriene C4 were significantly increased after NAPT in the patients diagnosed as LAR. This is in accordance with findings from other studies^(12,26) and indicative of LAR being a Th2 driven nasal mucosa inflammation, as both ECP and leukotriene C4 are Th2-mediated inflammatory markers⁽²⁶⁾. Although histamine is not a classic Th2 inflammatory marker, it has been shown to be a main mediator during the rapid early phase reaction of rhinitis⁽²⁷⁾. In this study, 12 patients had significantly higher levels of histamine compared to baseline levels following stimulation with allergen solution. We also observed that the patients had the classical symptoms of nasal irritation, which corresponds to the high level of histamine. For the remaining 60 patients in the cohort, even though they had negative serum sIgE results and positive local eosinophils results, these patients did not have positive local sIgE findings. Thus, according to the former diagnostic criteria⁽²⁷⁻²⁹⁾, these patients could be diagnosed as non-allergic rhinitis with eosinophilic syndrome (NARES) patients. However, this needs to be confirmed in further investigations. The findings of the present study are somewhat limited because of the relatively small number of patients. An earlier study in 2014 reported that LAR affects 25.7% of the rhinitis population⁽¹⁰⁾. This prevalence of LAR is quite high, compared to the present cohort, in which only 12/212 patients (5%) met the criteria of LAR during screening. This might be explained by the ethnic differences of the cohorts because most previous studies of LAR to date have been performed in Caucasians in Europe.

Conclusion

In conclusion, the present study suggested that measurement of local sIgE levels in nasal secretion, instead of NAPT, is a reliable and effective clinical method for a diagnosis LAR. However, these results need to be confirmed in a much larger cohort in a multicenter study and in multi-ethnic patients.

Acknowledgements

This work was supported by grants from National Key R & D Program of China (2016YFC20160905200), the program for Changjiang Scholars and Innovative Research Team (IRT13082); National Science Fund for the Major International Joint Research Program (81420108009); National Natural Science Foundation of China (81630023, 81100704, 81441029, 81441031, 81570894, 81400444, and 81470678); Capital Health Development Foundation (2016-1-2052).

Authorship contribution

YM prepared the manuscript and performed the statistical analysis. YW, HL, KW and NM collected the clinical data and samples. CW participated in collection of the clinical data and samples, and was involved in the preparation of the manuscript. LZ designed the study and participated in the interpretation and discussion of the data.

Conflict of interest

No conflict of interest.

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