

Clinical Characteristics and Allergen Sensitization Patterns of Patients with Local Allergic Rhinitis in Southern China

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Keywords

Rhinitis · Nasal secretion · Specific IgE · Pollen allergens · Tryptase

Abstract

Background: Local allergic rhinitis (LAR) is characterized by the production of specific IgE (sIgE) in the nasal mucosa without evidence of systemic atopy. The characteristics of LAR in Caucasians have been well documented. LAR is understudied in China, with prevalence, patient demographics, symptomatology, and the allergen sensitization profile being poorly understood. The purpose of this study is to investigate the demographics, characteristics, and allergen sensitization profile of patients with LAR in Southern China. **Methods:** A total of 194 patients with rhinitis and 13 healthy subjects were enrolled in the current study. The patients' demographic data, clinical history, and symptoms were recorded. Local and systemic sIgE to a wide panel of specific allergens were measured in the nasal secretion and serum samples. **Results:** Among the rhinitis patients, 115 were classified as allergic rhinitis (AR; 59.3%), 15 as LAR (7.7%), and 64 as non-AR (33.0%). The demographic characteristics, duration, frequen-

cy, and severity of symptoms were similar, although LAR exhibited higher symptom scores for nasal itch. Monosensitization was the predominant pattern of sensitization in both AR (109 out of 115, 95%) and LAR (14 out of 15, 93%). House dust mite was the dominant allergen in AR patients (109 out of 115, 95%), while pollen was the dominant allergen in LAR patients (11 out of 15, 73%). **Conclusion:** The prevalence of LAR patients in Southern China was 7.7%. Pollen was the most common sensitizing allergen for the local LAR patients, which differs from Caucasian studies, in which house dust mite was the dominant sensitizing allergen. Monosensitization was the predominant pattern in both AR and LAR.

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Introduction

Local allergic rhinitis (LAR) is a subtype of allergic rhinitis (AR) with positive allergen-specific IgE (sIgE) in nasal secretions and/or a positive nasal allergen provocation

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test but negative skin prick test (SPT) and/or serum sIgE. This subtype of rhinitis reflects the allergic condition of the nasal mucosa in individuals without systemic sensitization. This would previously have been classified as idiopathic rhinitis (IR). Non-AR (NAR) is defined as the clinical presence of rhinitis in the absence of both systemic and local atopy. The typical person with LAR is a nonsmoker, more often female, has severe persistent perennial rhinitis, which may be accompanied with conjunctivitis and asthma, and is sensitized to *Dermatophagoides pteronyssinus* (Der p) [1]. The prevalence rate of LAR can reach 25.7% of rhinitis subjects, and 25–62.5% in patients with IR [2–5]. The above studies were carried out in Caucasians in European countries. The prevalence of LAR in IR patients in other populations has also been reported: 8.2% in eastern China, 10.9% in Korea [6, 7], and 84.6% in Saudi Arabia [8]. The difference in prevalence rates indicates that genetic and environmental factors could affect the incidence of LAR.

The prevalence of rhinitis in mainland China has increased in recent years due to environment and lifestyle changes. Only one study has reported the evidence that LAR existed in Chinese subjects [7]. That study showed there was no difference between LAR and NAR patients with regard to the clinical symptoms, which was in contrast to findings in Caucasian patients. Furthermore, only one type of allergen (Der F) was evaluated in the patients and there was a lack of other common allergen sensitization information, and, finally, no local sIgE was examined in the nasal secretion. Hence, the clinical phenotypes of LAR in Chinese subjects remain to be further clarified and LAR is still underdiagnosed in the ear, nose and throat (ENT) clinic in China. The current study aimed to determine the characteristics of LAR in Chinese rhinitis subjects living in the southern part of China in order to provide a more accurate diagnosis and better management for LAR patients.

Materials and Methods

Study Subjects

This study was conducted at the Department of Otorhinolaryngology of the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, from March 2016 to March 2017. Patients with rhinitis symptoms were recruited into the study and were classified into 3 subtypes: AR, LAR, and NAR. Thirteen healthy subjects were included as a control group. AR patients had at least 1 symptom of nasal obstruction, nasal itching, sneezing and rhinorrhea (of a duration greater than 3 months) and positivity to SPT and serum sIgE test. The classification of LAR required at least 1 of the abovementioned nasal symptoms and positive nasal sIgE, but a

negative SPT and serum sIgE test. The classification of NAR required at least 1 of the abovementioned nasal symptoms and negative systemic and local sIgE. Healthy subjects should have no allergic or nasal diseases and be negative for both systemic and local sIgE. All rhinitis and control subjects were from the southern part of China (Guangdong, Guangxi, and Hainan provinces). The exclusion criteria were patients with chronic rhinosinusitis with or without nasal polyps, septal deviation, nasal tumors, acute upper respiratory tract infection, mental incapacity, and autoimmune or any other significant systemic diseases. In addition, all enrolled subjects were without intranasal/oral corticosteroids and antihistamine treatment for 14 days before recruitment. The study was conducted according to the principles of the Declaration of Helsinki, and was approved by the ethics committee of the Sun Yat-Sen hospital. Written informed consent was obtained from all participating subjects.

Demographic and Clinical Assessment

Demographic information, family history of atopy, smoking history, the presence of nasal and ocular symptoms, evaluation of symptom score, and comorbidities were documented for all subjects. In accordance with the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines [9], all rhinitis patients (AR, LAR, NAR) were classified as either persistent or intermittent, depending on the disease duration. For persistent rhinitis, symptoms lasted for more than 4 days a week and 4 weeks a year; for intermittent rhinitis, symptoms lasted for less than 4 days a week and 4 weeks a year. The severity of rhinitis was evaluated based on the symptoms affecting the items, including daily activities, work or school performance, and sleep, modified by the ARIA guidelines. Symptom severity was graded as mild (no affected items), moderate (any 1 or 2 of the affected items), and “severe” (all 3 affected items). The nasal or ocular symptom scores were evaluated using a visual analogue scale (VAS) where “score 0” meant “overall symptoms not at all bothersome” and “score 10” meant “overall symptoms extremely bothersome” according to the ARIA guideline [9]. All patients were coded confidentially and the VAS was analyzed independently by a clinician in a blinded manner.

Skin Prick Test

SPT was performed using house dust mite (*Dermatophagoides farinae*; 1 mg/mL; Wolwobiotech, Wuhan, China). Histamine (1.7 mg/mL) and saline were used as positive and negative controls, respectively. When the wheal area reached 25% of the positive control's area, it was considered as a positive response. Patients did not receive any drug treatment for at least 7 days before the test.

Serum sIgE Assay

The serum sIgE test was performed with a wide panel of locally prevalent allergens: *D. pteronyssinus*, *D. farinae*, a weed pollen mix (dwarf ragweed, *Artemisia*, *Humulus scandens*, *Chenopodium album*), and a mold mix (*Penicillium notatum*, *Cladosporium*, *Aspergillus fumigatus*, *Aspergillus niger*, *Alternaria*). sIgE in serum was determined by the ALLERG-O-LIQ allergen detection system (Fooke, Borken, Germany). The measurement range of the sIgE varied from 0.35 to 200 U/mL and was classified into 6 levels: level 0, <0.35 U/mL; level 1, 0.35–0.7 U/mL; level 2, 0.7–3.5 U/mL; level 3, 3.5–17.5 U/mL; level 4, 17.5–50 U/mL; level 5, 50–100 U/mL; and level 6, >100 U/mL. The positive cutoff value was 0.35 U/mL.

Table 1. Demographic and clinical data about the patients

	AR	LAR	NAR	Healthy controls
Subjects	115	15	64	13
Age, years ¹	18.0 (13.0–31.0)	34.0 (24.0–43.0)	37.0 (27.0–45.0)	25 (24.0–27.0)
<14 years	34 (29.6)	1 (6.7)	5 (7.8)	0 (0)
14–20 years	30 (26.1)	1 (6.7)	4 (6.3)	1 (7.7)
21–30 years	22 (19.1)	3 (20.0)	13 (20.3)	11 (84.6)
31–40 years	15 (13.0)	6 (40.0)	17 (26.6)	1 (7.7)
>40 years	14 (12.2)	4 (26.6)	25 (39.0)	0 (0)
Gender ²				
Male	70 (60.9)	7 (46.7)	26 (40.6)	6 (46.2)
Female	45 (39.1)	8 (53.3)	38 (59.4)	7 (53.8)
Dwelling				
City	72 (62.6)	10 (66.7)	49 (76.6)	13 (100)
Country	43 (37.4)	5 (33.3)	15 (23.4)	0 (0)
Comorbidities				
Asthma	18 (15.7)	3 (20.0)	10 (15.6)	0 (0)
Conjunctivitis	31 (27.0)	5 (33.3)	14 (21.9)	0 (0)
Family history of atopy	44 (38.3)	8 (53.3)	19 (29.7)	1 (7.7)
Smoking	8 (7.0)	0 (0)	12 (18.8)	0 (0)

Data are presented as *n* (%) or median (25–75%). AR, allergic rhinitis; LAR, local allergic rhinitis; NAR, non-allergic rhinitis. ¹ The difference in age was significant between the AR and NAR groups ($p < 0.001$), and AR and LAR groups ($p = 0.012$). ² The gender ratio was significantly different between the AR and NAR groups ($p = 0.009$).

Nasal sIgE Assay

The local sIgE to the same panel of aeroallergens evaluated in the serum sIgE test was determined in the nasal secretion using the IgE detection system described above (Fooke). A sinus pack (2 × 1 × 0.5 cm) was placed for 10 min in the nasal common meatus to absorb nasal secretions. To facilitate the extraction of nasal secretions, 0.5 mL of saline was added to the sinus pack, which was then stored at 4°C.

Nasal Tryptase Level

The measurement of tryptase in nasal secretions was performed using an enzyme-linked immunosorbent assay (ELISA) system (Raybiotech, Norcross, GA, USA).

Nasal Allergen Provocation Test

The nasal allergen provocation test (NAPT) was performed in symptom-free LAR ($n = 6$) and NAR patients ($n = 6$). Before the allergen provocation, patients were assessed for their nasal symptoms (rhinorrhea, obstruction, itching, and sneezing) using the VAS. The degree of nasal obstruction was evaluated by anterior rhinomanometry, and the eosinophil number was observed by nasal smear. Firstly, patients were challenged with saline to exclude a nonspecific nasal hyperreactivity. Then the nasal challenges with allergen extract were performed (house dust mite mix, 22 mg/mL; weed pollen mix, 50 mg/mL; or mold mix, 40 mg/mL). Thirty minutes later, the VAS of symptoms, nasal airflow resistance, and eosinophil change in the nasal smear were reevaluated. A positive

NAPT was considered to be an increase >30% in the total VAS, accompanied with an increase >100% in total airway resistance at 150 Pa, or an increase >15% in eosinophil ratio in the nasal secretion smear. All these LAR patients showed a positive NAPT response (2 allergic to house dust mite, 3 allergic to pollen, and 1 allergic to mold) and none of the NAR patients showed a positive reaction to the test (for house dust mite).

Statistical Analysis

Statistical analysis was performed using the SPSS 20 software. The data are presented as the median (25–75%), discrete numbers, and ratios. Continuous variables were analyzed by the Kruskal-Wallis test as the data did not follow a normal distribution. The χ^2 test, Yale continuity-corrected χ^2 test, and Fisher exact test were used for qualitative variables. Correlations were evaluated by the Kendall correlation coefficient test. A value of $p < 0.05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics

Among the rhinitis patients, 115 were classified as AR (59.3%), 15 as LAR (7.7%), and 64 as NAR (33.0%). The demographic and clinical characteristics of the subjects are described in Table 1. There was no significant differ-

Table 2. Clinical evaluation of patients in the AR, LAR, and NAR groups

	AR (<i>n</i> = 115)	LAR (<i>n</i> = 15)	NAR (<i>n</i> = 64)	<i>p</i> value (AR vs. LAR)	<i>p</i> value (LAR vs. NAR)
Disease duration					
<5 years	54 (47.0)	7 (46.6)	29 (45.3)	0.878	0.660
5–10 years	25 (21.7)	4 (26.7)	11 (17.2)		
≥10 years	36 (31.3)	4 (26.7)	24 (37.5)		
Persistence of symptoms					
Intermittent	20 (17.4)	6 (40.0)	18 (28.1)	0.078	0.369
Persistent	95 (82.6)	9 (60.0)	46 (71.9)		
Severity of symptoms					
Mild	18 (15.7)	3 (20.0)	22 (34.4)	0.710	0.365
Moderate to severe	97 (84.3)	12 (80.0)	42 (65.6)		
Nasal symptoms					
Sneezing	6.0 (5.0–9.0)	6.0 (5.0–9.0)	6.0 (4.0–9.0)	0.997	0.668
Rhinorrhea	6.0 (4.0–9.0)	6.0 (2.0–8.0)	7.0 (3.3–9.0)	0.164	0.137
Nasal blockage	4.0 (2.0–8.0)	6.0 (3.0–9.0)	4.0 (2.0–7.8)	0.084	0.109
Nasal itching	5.0 (3.0–8.0)	8.0 (3.0–9.0)	4.0 (3.0–6.0)	0.095	0.009*
TNSS	21.0 (17.0–27.0)	24.0 (20.0–29.0)	21.0 (15.0–26.8)	0.226	0.187
Ocular symptoms					
Eye itching	3.0 (0–5.0)	3.0 (0–6.0)	0 (0–4.0)	0.956	0.083
Eye watery	1.0 (0–4.0)	3.0 (0–5.0)	0 (0–3.0)	0.357	0.133
Eye erythema	0 (0–0)	0 (0–3.0)	0 (0–0)	0.022*	0.011*
TOSS	5.0 (2.0–9.0)	6.0 (3.0–14.0)	3.0 (0–7.8)	0.106	0.004*

Data are presented as *n* (%) or median (25–75%). The Kruskal-Wallis test was used for continuous variables and the Bonferroni test was used for the comparison of two groups. The Fisher exact test was used for qualitative variables. **p* < 0.05. AR, allergic rhinitis; LAR, local allergic rhinitis; NAR, non-allergic rhinitis; TNSS, total nasal symptom score; TOSS, total ocular symptom score.

Table 3. Allergens tested in SPT, serum sIgE, and nasal sIgE

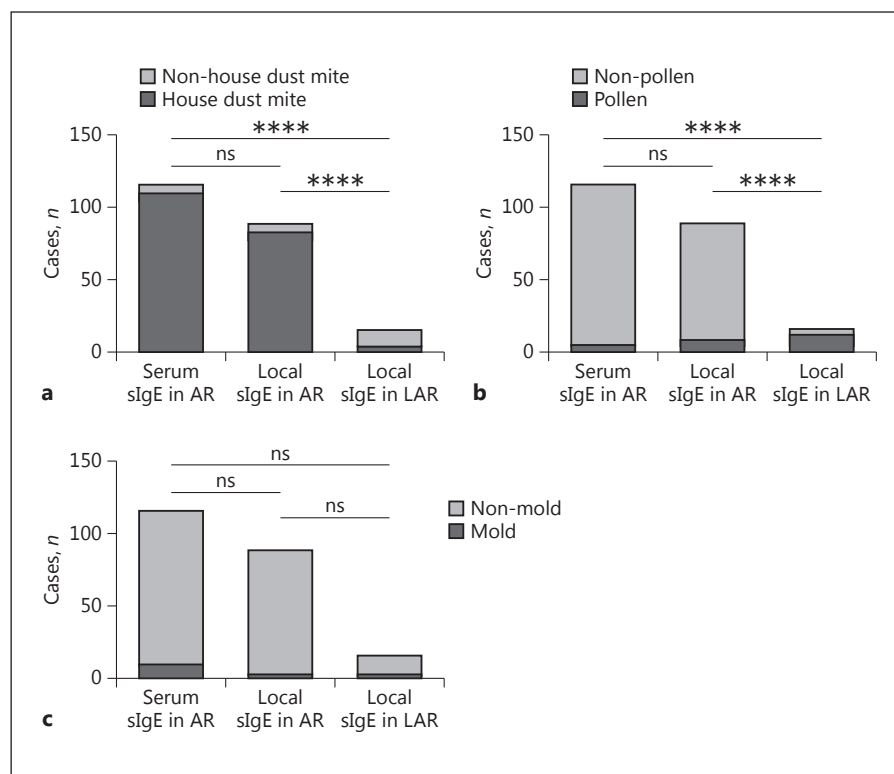
	SPT Der f	Serum sIgE positive				Nasal sIgE positive			
		Der p	Der f	pollen	mold	Der p	Der f	pollen	mold
AR (<i>n</i> = 115)	106	107	107	4	9	75	78	7	2
LAR (<i>n</i> = 15)	0	0	0	0	0	1	3	11	2
NAR (<i>n</i> = 64)	0	0	0	0	0	0	0	0	0
Control (<i>n</i> = 13)	0	0	0	0	0	0	0	0	0

AR, allergic rhinitis; LAR, local allergic rhinitis; NAR, non-allergic rhinitis.

ence in most demographic or clinical information between the AR, LAR, and NAR groups, except that the mean age was lower in the AR group (mean age 18 years) as compared to LAR subjects (mean age 34 years; *p* = 0.012) or the NAR group (mean age 37 years; *p* < 0.001). Unlike the Caucasian studies, showing a female predominance in the LAR group, the gender ratio was more equal among Chinese patients.

The clinical characteristics of the patients are shown in Table 2. With regard to the disease duration, symptom frequency, and symptom severity, there was no significant difference between the AR, LAR, and NAR groups. The score of nasal itching in the LAR group was 2-fold higher than in the NAR group (*p* = 0.009), while the scores for eye erythema and total ocular symptoms were higher in the LAR group as compared to the NAR group. The

Fig. 1. The rates of positive serum sIgE in AR, local sIgE in AR (from the local sIgE-positive subjects, $n = 79$), and local sIgE in LAR were compared for house dust mite (a), pollen (b), and mold (c). ns, not significant. **** $p < 0.0001$.



severity of other individual nasal or ocular symptom tended to be similar between the LAR and AR groups, except for eye erythema ($p = 0.022$).

Allergen Sensitization Patterns in Patients with AR and LAR

Four types of major aeroallergens were measured in the serum and nasal secretion from patients with AR, LAR, and NAR, and the control groups, including Der p, Der f, the weed pollen mix, and mold mix (Table 3). Monosensitization was the predominant aeroallergen pattern in both AR (109 out of 115, 95%) and LAR (14 out of 15, 93%) patients, but the sensitizing allergen was significantly different between these two groups: house dust mite (Der p, Der f, or both) was the dominant allergen in AR patients (109 out of 115, 95%), while pollen was the dominant allergen in LAR patients (11 out of 15, 73%; Fig. 1). The local sIgE levels in AR patients were also evaluated and the positive rate was 77% (88 out of 115); among them, 92% (82 out of 88) of the patients were sensitized with house dust mite (Fig. 1). Therefore, the sensitization pattern of LAR was distinct from that of AR regardless of the serum or local secretion level.

sIgE Levels in Nasal Secretions in the Different Groups

sIgE levels of Der p, Der f, pollen, and mold in nasal secretion were compared across the AR, LAR, NAR, and control groups. sIgE of Der p and Der f in the AR group was significantly higher than that in the LAR, NAR, and control groups (Fig. 2). By contrast, the LAR group showed a significantly higher sIgE level of pollen than the other three groups (AR, NAR, and controls; Fig. 2). There was no difference in the mold sIgE amount between the four groups.

Tryptase Levels in Nasal Secretion

The local levels of tryptase in nasal secretion were measured in the AR, LAR, and NAR groups. Although the concentration of tryptase were higher in the AR (28.50 ng/mL) and LAR (34.15 ng/mL) groups compared to the NAR group (22.23 ng/mL), there was no statistically significant difference. Correlation analysis for tryptase between symptom scores was further performed. Nasal tryptase levels were positively correlated with the severity of subjective nasal obstruction in patients with AR ($r = 0.445$, $p = 0.001$) and NAR ($r = 0.280$, $p = 0.037$), but local tryptase levels were not significantly associated with other nasal or ocular symptoms (Table 4).

Fig. 2. sIgE levels of different allergens in nasal secretion were compared between the AR, LAR, NAR, and control groups. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

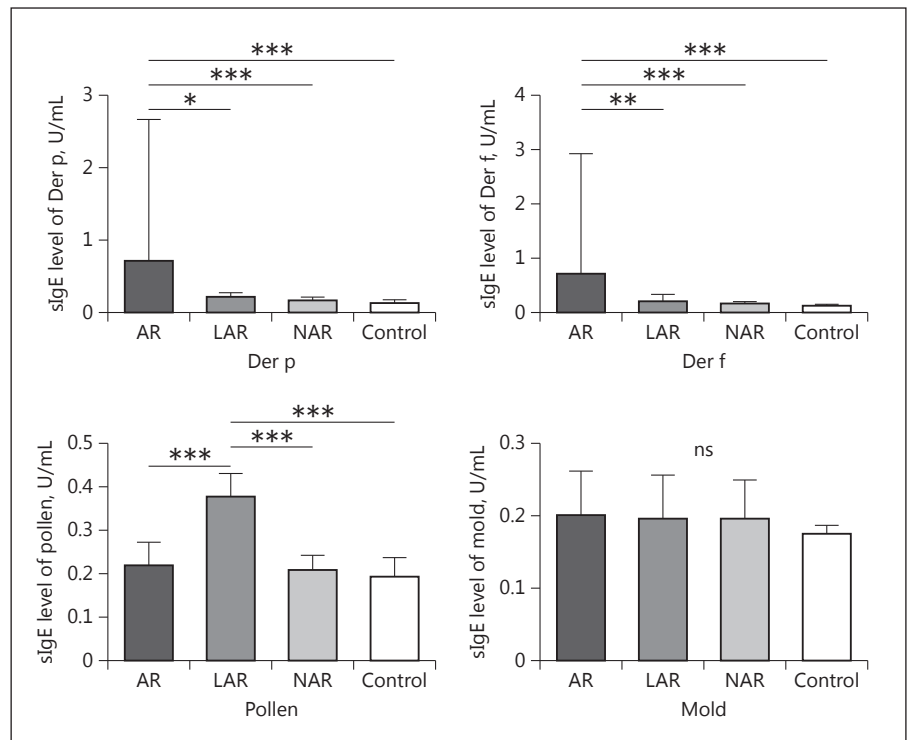


Table 4. Correlation between nasal symptom scoring and nasal tryptase in AR, LAR, and NAR subjects

Symptom scoring	AR (<i>n</i> = 28)		LAR (<i>n</i> = 8)		NAR (<i>n</i> = 30)	
	<i>r</i> value	<i>p</i> value	<i>r</i> value	<i>p</i> value	<i>r</i> value	<i>p</i> value
Sneezing/tryptase	0.003	0.984	−0.231	−0.441	0.080	0.552
Rhinorrhea/tryptase	−0.062	0.659	−0.109	0.708	−0.142	0.293
Nasal blockage/tryptase	0.445	0.001*	−0.473	0.105	0.280	0.037*
Nasal itching/tryptase	0.251	0.077	−0.074	0.802	0.005	0.97
TNSS/tryptase	0.216	0.113	−0.143	0.621	0.077	0.555

AR, allergic rhinitis; LAR, local allergic rhinitis; NAR, nonallergic rhinitis; TNSS, total nasal symptom score. * Statistically significant.

Discussion

The current studies demonstrated the patterns and phenotypes of LAR patients from mainland China, where there is a dearth of research in LAR, with only 1 existing study in Chinese patients [7]. We found that the proportion (19.0%) of LAR among the IR subjects in our study was lower than the results reported in Western countries (e.g., Spain 54–62.5%) but similar to other Asian countries (e.g., Korea 10.8%) [3, 4, 6].

The features of LAR in Chinese patients in our study were largely consistent with those reported in Caucasian

populations with regard to the symptom severity and frequency, as well as having nasal itch and watery rhinorrhea as the main nasal symptoms. However, Chinese patients with LAR present a distinct clinical characteristic of allergen sensitization compared to Caucasians, and we found that pollen was the dominant sensitizing allergen. The most interesting finding in our study was that pollen, and not Der f/Der p, is the most commonly sensitized aeroallergen in LAR patients from Southern China. This is in contrast to Der f/Der p being the dominant sensitized aeroallergen in Caucasian LAR patients [1] and in Chinese AR patients. The difference in sensitizing allergen

between AR and LAR is intriguing and warrants further study.

In the other study on LAR in Chinese patients, Cheng et al. [7] measured the Der f level after NAPT and found that 8.2% of patients (12 out of 147) among the IR subjects were considered to have LAR. However, that study did not evaluate the other major aeroallergens (such as pollen and molds) and local sIgE or tryptase levels in the nasal secretion. In the current study, we have described more comprehensive information about the phenotypes of LAR in patients from Southern China, assessed a comprehensive panel of aeroallergens, including pollen and molds, and found that pollen was the most prevalent sensitizing allergen in LAR. This finding has important diagnostic implications as Chinese clinicians need to be aware of the fact that pollen is an important aeroallergen in LAR and that there is a need to test for it.

AR and LAR share similar symptoms, but it has been demonstrated that these are two different entities [10]. In ENT or allergy clinics in China, the awareness and understanding of LAR among clinicians are less than ideal and, as such, LAR is very likely to be underdiagnosed. It should be highlighted that patients with AR symptoms but without positive systemic sIgE need to be examined for local sIgE levels, in order to make the differentiation between LAR and NAR. This has therapeutic implications. A recent clinical trial of subcutaneous allergen (Der p) immunotherapy conducted in a cohort of LAR patients found that immunotherapy was efficacious in LAR patients

[11]. Therefore, the diagnosis and identification of the allergen in LAR patients are critical in guiding the management of this group of patients. A potential obstacle in diagnosis is the limited availability of nasal provocation tests in Chinese ENT and allergy clinics, and testing for sIgE or tryptase may not be practical in many clinics.

In conclusion, the current study demonstrated the clinical characteristics and phenotypes of patients with LAR in Southern China, and showed that pollen is a more common sensitizing aeroallergen than house dust mite in LAR, which is distinct from the findings reported in Caucasian populations. Follow-up studies and the examination of molecular alteration underlying LAR in Chinese patients should be performed in the future.

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Disclosure Statement

None of the authors have conflicts of interest to declare.

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