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Original Manuscript

American Journal of Rhinology & Allergy
1–7
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DOI: 10.1177/19458924211037913
journals.sagepub.com/home/ajr
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The Importance of Nasal Provocation Testing in the Diagnosis of *Dermatophagoides pteronyssinus*-Induced Allergic Rhinitis

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Abstract

Background: Allergen identification is the first step for allergen-specific immunotherapy (AIT) of allergic rhinitis (AR). Currently, the diagnosis of AR is based mainly on the positive results of the skin prick test (SPT) and/or serum specific immunoglobulin E (sIgE) measurement. However, the results of these two tests may not always directly correlate with AR.

Objective: To investigate the importance of nasal provocation testing (NPT) in the diagnosis of *Dermatophagoides pteronyssinus* (Der p)-induced AR.

Methods: Rhinitis patients willing to undergo AIT (n = 171) were enrolled. The correlations of Der p SPT, sIgE, NPT, and clinical symptom severity were assessed.

Results: NPT-positive responses were more common in patients with higher SPT and sIgE levels. The optimal cut-off value for a NPT-positive response for SPT was 5.5 mm and for sIgE was 2.77 kUA/L, based on the respective receiver operating characteristic (ROC) curves. The area under the curve (AUC) of the ROCs was 0.814 (SPT only) and 0.794 (sIgE only) and increased to 0.828 with the combination of SPT and sIgE. The Der p-NPT concentration was inversely correlated with SPT and sIgE levels ($r = -0.477$, $P < .001$, and $r = -0.461$, $P < .001$, respectively), but none was correlated with the total nasal symptom score.

Conclusion: For patients who are willing to receive Der p AIT, NPT is a useful and safe test to confirm diagnosis prior to treatment initiation, especially in patients with lower levels of Der p SPT (< 5.5 mm) or sIgE (< 2.77 kUA/L).

Keywords

nasal provocation testing, *Dermatophagoides pteronyssinus*, allergic rhinitis, skin prick test, serum-specific IgE

Introduction

Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated inflammatory disorder of the nasal mucosa that is mainly characterized by repeated rhinorrhea, sneezing, nasal pruritus, and congestion. This condition currently affects 10% to 40% of the population worldwide, seriously affecting the quality of life of patients and causing significant socioeconomic burdens.[1] According to an epidemiological survey conducted on AR in China, the self-reported prevalence of AR increased from 11.1% in 2005 to 17.7% in 2011.[2]

In addition to the typical clinical symptoms and manifestations, the diagnosis of AR is based mainly on the positive results of the skin prick test (SPT) and/or serum specific immunoglobulin E (sIgE) measurement. However, the positive results of these tests manifest only the presence of sIgE *in vivo* but do not directly correlate with AR. Supakthanasiri et al[3] demonstrated that 42% of asymptomatic individuals have positive SPT results. For patients with local allergic rhinitis (LAR),[4] allergen sIgE is found only in the local nasal mucosa, while SPT and sIgE showed negative results. Moreover, disagreement between SPT and sIgE has been shown by many previous studies.[5–8] For example, Nam and Lee[8] recently revealed that the overall agreement between SPT and sIgE was only 75.3%. All these findings suggested that allergen diagnosis based on SPT and/or serum sIgE results might be unable to distinguish AR, nonallergic rhinitis (NAR), and LAR patients, resulting in misdiagnosis or missed diagnosis. Especially for patients willing to accept allergen-specific immunotherapy (AIT), SPT and

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sIgE measurements might not meet the clinical requirements for determining allergens.

Nasal provocation testing (NPT) refers to the direct application of an allergen to the nasal mucosa under standard and controlled conditions to observe whether allergens can provoke an immediate type I immune reaction and evoke cardinal symptoms of rhinitis.[9] It is a safe and straightforward technique and recommended in order to identify rhinitis phenotypes or to identify those allergens against which AIT is a promising option.[10,11]

House dust mites (HDMs) are the most common aeroallergens that cause AR and asthma in mainland China.[12] The purpose of this study was to investigate the importance of NPT in the diagnosis of *Dermatophagoides pteronyssinus* (Der p)-induced AR before AIT recommendations.

Methods

Study Participants

Patients with rhinitis who would accept HDM AIT (n = 171) were enrolled. All patients (aged 5-60 years) had at least a 1-year history of rhinitis symptoms, underwent SPT and sIgE evaluation, and had positive results of SPT and/or sIgE for Der p. However, if the patients had negative results of SPT and sIgE for Der p, but the clinical history suggested that the symptoms might be induced by HDMs, they were also included. Then, NPT was performed. Pregnant women, patients who were treated with AIT, and those who had positive SPT and/or sIgE results to other allergens besides mites were excluded. In addition, for patients with a clinical history of asthma, FEV1% should be $\geq 80\%$ before NPT. This study was approved by the ethical committee of West China Hospital, Sichuan University, and we obtained written informed consent from all subjects.

Clinical History

The detailed clinical history of the patients was collected, which included age, gender, disease course, factors that induce or aggravate symptoms, and asthma history. Disease severity was classified as mild and moderate/severe according to the Allergic Rhinitis and its Impact on Asthma guidelines.[1] The severity of symptoms was evaluated by the total nasal symptom score (TNSS) by categorizing them as follows: 0 to 4 = mild, 5 to 8 = medium, and 9 to 12 = severe.

Skin Prick Test

Twelve common allergens, namely, Der p, *Dermatophagoides farina* (Der f), cat, dog, cockroach, *Alternaria, Cladosporium cladosporioides*, *Humulus*, *Artemisia*, *Broussonetia*, *Cupressaceae* and *Betula*, were tested. Histamine (10 mg/ml) and diluent were used as positive and negative controls, respectively. The allergen extracts of Der p, Der f, and control solutions were obtained from ALK. The remaining extracts were obtained from the PUMC-Pharma Link Company. SPT was performed on the volar side of the forearm. A positive skin reaction was defined as a wheal size of 3 mm greater than that of the negative control. In addition, a positive score based on the wheal size was recorded as follows: Class 1: a wheal diameter between 3 and 5 mm; Class 2: a wheal diameter between 5 and 10 mm; Class 3: a wheal diameter between 10 and 20 mm; and Class 4: a wheal diameter ≥ 20 mm and present with pseudopods.[13]

Serum IgE Analysis

Serum Der p sIgE was measured by the UNICAP System (Thermo Fisher). sIgE analysis was defined as positive if the measurement was ≥ 0.35 kUA/L, and the results were divided into 7 levels from 0 to 6 (0, 0.1-0.35 kUA/L; I, 0.35-0.70 kUA/L; II, 0.70-3.50 kUA/L; III, 3.50-17.5 kUA/L; IV, 17.5-50.0 kUA/L; V, 50.0-100 kUA/L; and VI, > 100 kUA/L).

Nasal Provocation Testing

Before undergoing NPT, any drug that modified the nasal response was discontinued (such as oral antihistamines: 1 week, topical antihistamines: 5 days, nasal corticosteroids: 3 days), and the patient had to be asymptomatic or have only mild symptoms that did not interfere with the test results. The test was postponed for at least 2 to 4 weeks after exacerbation of AR.[14] Subjective symptom scores were assigned according to the Lebel score.[15] Objective assessment of nasal resistance was performed by rhinomanometry (GM Instruments Ltd). NPT was considered positive if the total symptom score was ≥ 5 and nasal resistance at 150 Pa was increased $\geq 100\%$.[14] After baseline assessment, the better nasal ventilation side was selected for the application of diluent (0.2% phenol and 0.9% saline, Shanxi Taiyuan Pharmaceutical Link Company) and Der p allergen (neat solution 0.35 mg/ml, PUMC-Pharma Link Company).[14,16] The solution was delivered toward the inferior turbinate through a nebulizer with a fixed volume of 100 µl per puff. First, 100 µl of diluent was given to evaluate nasal hyperreactivity. If nonspecific hyperresponsiveness was absent, increasing concentrations of Der p allergen extract (1/100, 1/10, neat solution) were applied to one nostril at 15 min intervals. Patients with a clinical history of asthma were carefully monitored for peak expiratory flow during testing.

Statistical Analysis

SPSS version 21.0 was used for statistical analysis. The clinical features, such as gender, age, clinical history, and so on, of NPT-positive and NPT-negative patients were compared using the chi-square test or Mann–Whitney *U* test.

Table 1. General Clinical Features of Participants.

	NPT (+) (N = 120)	NPT (−) (N = 51)	Statistical value	*P*
Age (years, median [IQR])	24.50 [11.00,30.75]	27.00 [16.00,38.00]	$Z = -1.927$	.054
Gender (M/F)	53/67	25/26	$X^2 = 0.340$	.560
Disease course (years, median [IQR])	6.00 [3.00,10.00]	6.00 [3.00,10.00]	$Z = -0.158$	.875
Inducing factor				
Uncorrelated with HDMs	11 (9.2)	10 (19.6)	$X^2 = 3.622$	.057
Correlated with HDMs	109 (90.8)	41 (80.4)		
Without asthma	105 (87.5)	44 (86.3)	$X^2 = 0.048$	.827
With asthma	15 (12.5)	7 (13.7)		
Disease severity				
Mild	8 (6.7)	5 (9.8)	$X^2 = 0.501$	.479
Moderate/severe	112 (93.3)	46 (90.2)		
TNSS				
Mild	7 (5.8)	4 (7.8)	$Z = -0.317$	.752
Moderate	64 (53.3)	27 (52.9)		
Severe	49 (40.8)	20 (39.2)		

Abbreviations: NPT, nasal provocation testing; HDMs, house dust mites; TNSS, total nasal symptom score.

Thresholds, sensitivity, and specificity of the areas under the curve (AUCs) of SPT and sIgE in diagnosing Der p-induced AR were analyzed by receiver operating characteristic (ROC) curves. The correlations of SPT and sIgE levels with the concentration of positive Der p-NPT and the correlations of all the three tests with TNSS grades were analyzed by Spearman's test. *P* values < .05 were regarded as statistically significant.

Results

Patient Characteristics

In total, 171 patients were included. There were no statistically significant differences in demographic and clinical characteristics of the NPT-positive and NPT-negative groups ($P > .05$, Table 1).

Correlations of SPT and sIgE Levels and NPT

The results are summarized in Table 2. For patients with SPT results of class 0, 1, 2, 3, and 4, NPT-positive rates were 21.1%, 40%, 62.7%, 86.1%, and 100%, respectively. Additionally, for patients with sIgE results of class 0, 1, 2, 3, and above 4, NPT-positive rates were 23.3%, 50%, 70.6%, 85.3%, and 87.3%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) were 76.3% and 78.9% for SPT and 80.1% and 76.7% for sIgE, respectively. Moreover, in 17 patients without Der p sensitization according to the negative results of SPT and sIgE but who had a clinical history suggesting HDM induction of symptoms, 3 (17.6%) had positive responses to NPT. In addition, there were 15 (8.8%) patients with discordant results between SPT and sIgE, meaning that the patients had negative SPT results but positive sIgE results or vice versa. Among them, 5 (33.3%) had positive results for NPT.

Table 2. Results of SPT and sIgE Test After NPT.

	NPT		
	Negative	Positive	Total
SPT			
0	15	4	19
3 to 5 mm	3	2	5
5 to 10 mm	22	37	59
10 to 20 mm	11	68	79
≥ 20 mm	0	9	9
Total	51	120	171
sIgE class			
0	23	7	30
1	5	5	10
2	10	24	34
3	5	29	34
4	5	24	29
5	0	16	16
6	3	15	18
Total	51	120	171

Abbreviations: NPT, nasal provocation testing; SPT, skin prick test; sIgE, specific immunoglobulin E.

The optimal cut-off value of the ROC curve for SPT was 5.5 mm (with an optimized sensitivity and specificity of 92.5% and 64.7%, respectively), and the AUC was 0.814 (95% CI [0.739, 0.890], $P < .001$). The optimal cut-off value of the ROC curve for quantitative analysis of sIgE was 2.77 kUA/L (with an optimized sensitivity and specificity of 76.7% and 72.5%, respectively), and the AUC was 0.794 (95% CI [0.715, 0.873], $P < .001$). However, combined SPT and sIgE results revealed that the AUC

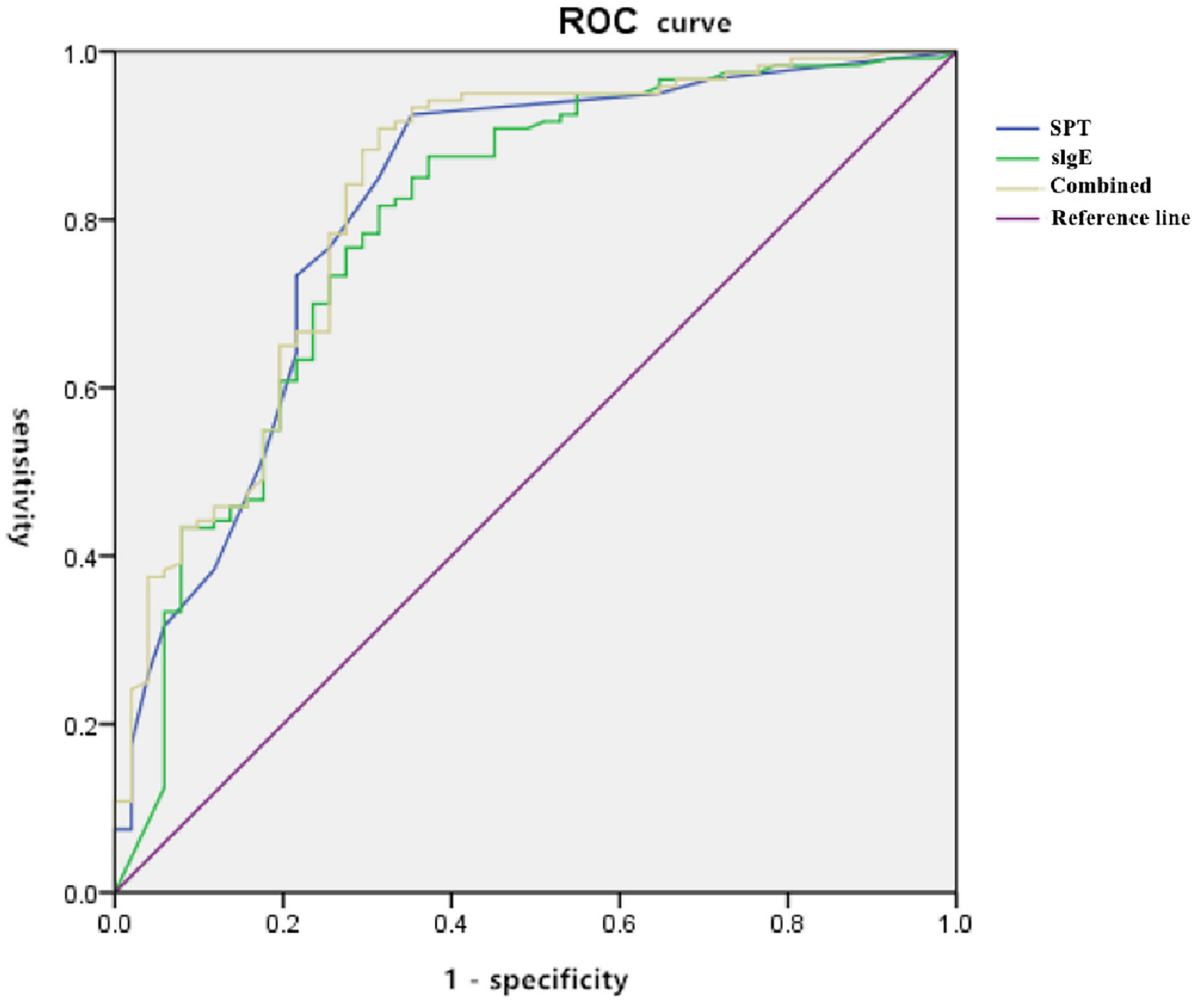

Figure 1. ROC curve of SPT sIgE level and combined of SPT and sIgE for diagnosing Der p-induced AR.
ROC, receiver operating characteristic; SPT, skin prick test; sIgE, specific immunoglobulin E; AR, allergic rhinitis.

was slightly elevated to 0.828 (95% CI [0.756, 0.899], $P < .001$) (Figure 1).

Correlations of SPT and sIgE Levels with the Concentration of Positive Der p-NPT

The concentration eliciting a positive response by NPT showed a negative correlation with the levels of SPT and sIgE ($r = -0.477$, $P < .001$, and $r = -0.461$, $P < .001$, respectively) and was shown by a percentage stacking bar chart (Figure 2(A) and (B)).

Correlations of SPT and sIgE Levels and Concentration of Positive NPT with TNSS Grades

There was no significant correlation of SPT and sIgE levels with TNSS grades. Moreover, the concentration eliciting a positive response by NPT also showed no correlation with TNSS grades ($P > .05$).

Discussion

The management of AR includes allergen avoidance, pharmacotherapy, AIT, and patient education, and allergen identification is the first step in AR management.[1] In the present study, three allergen diagnostic tests, including SPT, sIgE, and NPT, for diagnosing Der p in AR were used to investigate patients who required AIT for AR induced by HDMs, and their correlations with TNSS grades were analyzed.

In general, the PPV and NPV were 76.3% and 78.9% for Der p SPT and 80.1% and 76.7% for Der p sIgE, respectively. These results indicate that if deciding whether to apply AIT, according only to SPT or sIgE results, approximately one-quarter of patients may receive the wrong recommendation. In addition, NPT-positive responses were more common in patients with higher SPT and sIgE grades, which was in accordance with previously published studies.[17–19] The optimal cut-off values of the ROC curves of SPT and sIgE were 5.5 mm and 2.77 kU_A/L, respectively, in the present study, which indicated that if SPT < 5.5 mm or

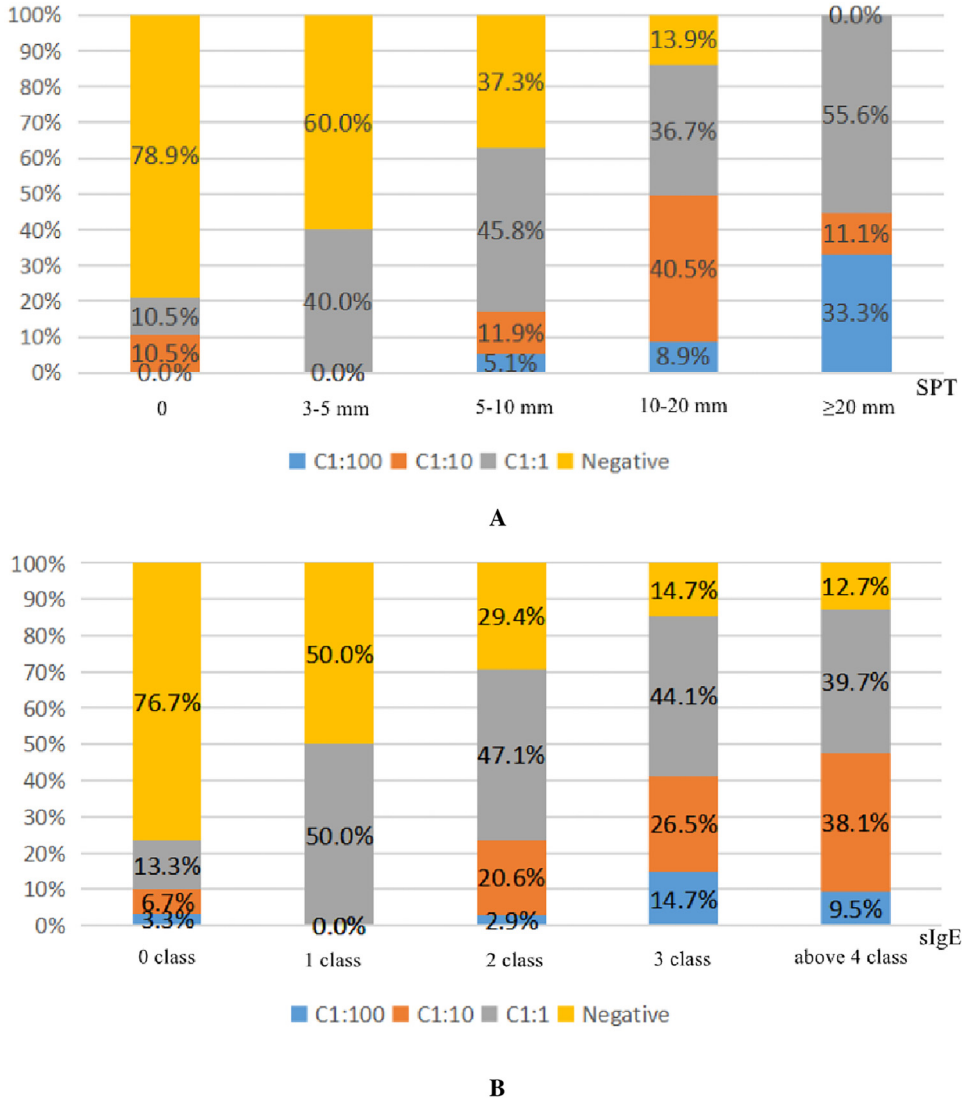

Figure 2. Correlations of SPT level (A) and sIgE level (B) with the correlation of positive Der p-NPT.
C1:100, C1:10, and C1:1 refer to the positive response of NPT elicited by 1:100, 1:10, and 1:1 concentrations of Der p, respectively, and the negative response refers to the negative NPT result.
SPT, skin prick test; sIgE, specific immunoglobulin E; NPT, nasal provocation testing.

sIgE < 2.77 kU_A/L, the results should be interpreted more cautiously because the positive results might not be relevant to the clinical symptoms.

According to a study conducted by Gabriele on dust mite-sensitized participants, there were only 58% of participants were both SPT and sIgE positive for HDMs, and 21% of HDM sensitizations were missed if sIgE or SPT evaluation alone had been performed. Therefore, the simultaneous use of both tests should be considered when aiming to determine AR in sensitized populations.[20] However, whether the combined use of SPT and sIgE can improve HDM-induced diagnostic accuracy is still a question in clinical practice. This study revealed that when SPT and sIgE were combined, the AUCs of the ROCs increased from 0.814 (SPT only) and 0.794 (sIgE only) to 0.828, so the diagnostic accuracy increased but to a limited extent. In addition, disagreement between SPT and sIgE is a common problem.[5–8] In the present study, 8.8% of patients had differences in the results between these two tests. In this situation, clinical decision-making became more difficult, and NPT was an especially beneficial indication and could provide precise information as part of the evaluation.

In our study, no statistically significant differences were observed in patients' impressions of whether HDM exposure induced or aggravated their symptoms between the NPT-positive and NPT-negative groups. This result suggested that clinical history might not be effective in predicting the Der p-NPT result. Currently, the diagnosis of AR is

based on allergic history, SPT and sIgE. For AR induced by seasonal allergens, such as pollen, as allergic episodes coincide with particular pollen seasons, the correlation between allergen exposure and clinical symptoms could be observed, thus making clinical diagnosis easier. For AR caused by perennial allergens, however, the correlation between allergen exposure and clinical symptoms can be obscure, making allergy history a less reliable diagnostic tool. In addition, the change in nonallergic factors, such as temperature or humidity, leads to symptoms that largely overlap with HDM-induced AR, and medical history cannot distinguish between allergic and nonallergic factors. Riechelmann et al compared the clinical history, SPT and sIgE with the results of NPT to confirm clinically relevant allergy to Der p in patients with chronic rhinitis and revealed that AR diagnosis based on allergic history, SPT and sIgE resulted in a false result rate of ~30%. Moreover, the frequency of clinical history information indicated worsening during HDM exposure, which was remarkably similar in patients with positive and negative NPTs.[17] Fernandez et al[21] also showed that the majority (78%) of patients with a positive bronchial provocation test to cat allergen did not think that cats triggered their allergies. These studies confirmed our suggestion that the subjective impression of the patient regarding the clinical history might not be reliable.

LAR is a new phenotype of AR that has recently led to significant interest among researchers. It is attributed to a localized allergic response in the nasal mucosa.[4,22] In the present study, 17 patients without Der p sensitization were detected by SPT and sIgE, 3 (17.6%) of whom demonstrated a positive response to Der p-NPT and could be diagnosed with LAR. Published literature states that up to 26.5% of patients who fulfil the diagnostic criteria for LAR are mistakenly classified as NAR.[23,24] Several studies from Asian countries reported a lower prevalence (4%-10.9%) of LAR than that in Western countries.[25–27] For diagnosing LAR, NPT is regarded as the gold standard due to its optimal sensitivity and specificity,[24,28–30] while the sensitivity of the measurement of nasal sIgE is considerably lower than that of NPT (positive in 20%-43% of LAR cases).[31–33] Although the mechanism of LAR is not entirely the same as that of AR, several randomized double-blind placebo-controlled clinical trials have demonstrated AIT as an effective treatment for LAR.[34–36] Therefore, for NAR patients whose clinical history suggests allergy, the possibility of LAR should be considered, and NPT can be integrated into the differential diagnosis to avoid missing AIT, which may be an effective approach in such cases.

Our study showed that although the concentration of positive Der p-NPT showed a significant correlation with the levels of SPT and sIgE in diagnosing Der p, none of the three tests showed any significant correlation with disease severity as assessed by subjective TNSS. This result was in accordance with the findings put forward by Matsumoto et al[37]. However, Wang et al's[19] study showed that Der p-NPT concentration was associated with the rhinoconjunctivitis quality of life questionnaire. Therefore, further studies are required to elaborate on whether Der p-NPT correlates with AR subjective severity assessment. However, such a challenge differs from the natural course of the disease in that it is a single provocation and does not reflect the real-life situation of HDM-induced AR, which is persistent with allergic triggering that interacts with ongoing inflammation.[38] This may be the reason why Der p-NPT showed no correlation with the subjective severity assessment.

Conclusion

Der p-NPT positive responses were more commonly observed in patients with higher Der p SPT and sIgE levels, and the Der p-NPT concentration was inversely correlated with the SPT and sIgE levels. For rhinitis patients who need Der p AIT, NPT is considered a useful and safe test to discriminate AR, NAR, and LAR prior to treatment initiation, especially in patients with lower levels of Der p SPT (< 5.5 mm) or sIgE (< 2.77 kUA/L).

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants to Juan Meng from the International Cooperation Project from Science and Technology of Sichuan Province (No. 2018HH0097), the 1·3·5 Project for Disciplines of Excellence-Clinical Research Incubation Project at West China Hospital of Sichuan University (No. 2018HXFH026), the Returned Overseas Chinese Scholars Science and Technology Project from Department of Human Resources and Social Security of Sichuan Province (No.(2020).291); Guo Liu from National Natural Science Foundation of China (No. 81800892).

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