

Responsiveness of Nasal Provocation Testing—But Not Skin Test and Specific Immunoglobulin E Blood Level—Correlates With Severity of Allergic Rhinitis in *Dermatophagoides* Species-Sensitized Patients

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Abstract

Background: The results of skin and blood allergen testing are not consistently relevant to clinical manifestations in allergic patients.

Objective: The aim of the study was to investigate the relationship between severity of allergic rhinitis and different allergen diagnostic tests in *Dermatophagoides* species-sensitized patients.

Methods: Study subjects included 65 rhinitis patients—50 with *Dermatophagoides pteronyssinus* (DP) sensitization (DP+) and 15 without DP sensitization (DP–), and 15 DP+ and 37 DP– healthy controls (HCs) confirmed by allergen skin prick (SPT) and blood specific immunoglobulin E (sIgE) tests. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was tested. All subjects underwent DP nasal provocation test (DP-NPT). Visual analogue scoring (VAS) of nasal symptoms and nasal airway resistance (NAR) were measured before and after NPT. Correlations between the 3 allergen tests and score of RQLQ were performed.

Results: All rhinitis subjects had significantly higher VAS and NAR after DP-NPT than HCs ($P < .01$). All DP+ rhinitis, 40% of DP– rhinitis subjects, 13.3% of DP+ HCs and 0% of DP– HCs had positive DP-NPT. Dose of positive DP-NPT positively correlated with SPT diameter and sIgE level in all tested subjects ($P < .001$). Score of RQLQ positively correlated with dose of DP-NPT ($P < .001$), but not with SPT diameter and sIgE level in rhinitis patients.

Conclusion: Although DP nasal provocation, skin prick wheal size and blood sIgE level correlate with each other, only nasal provocation testing is associated with severity of nasal symptoms. It is suggested that NPT should be performed to verify a clinically relevant allergy.

Keywords

Dermatophagoides sp., allergic rhinitis, RQLQ, nasal provocation testing, allergen diagnostic tests

Introduction

Allergic rhinitis (AR) involves hyperactive nasal mucosa; obstruction of the nasal passages; and symptoms of rhinorrhea, sneezing, nasal pruritus, and congestion.¹ It is an immunoglobulin E (IgE)-mediated inflammatory nasal disorder that develops when the immune system becomes sensitized and overreacts to air-borne allergens.¹ Although AR is often dismissed as a minor discomfort, it currently affects 10% to 25% of the

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population worldwide and has been found to have significant socioeconomic effects.¹

The diagnosis of allergic rhinitis is often made on the basis of clinical characteristics and response to pharmacotherapy.² Evidence of sensitization to a known allergen usually involves a combination of skin or blood testing and patient's exposure history.³ Although skin prick test (SPT) and serum specific IgE (sIgE) are standardized tests widely used in the diagnosis of suspected cases of IgE-mediated allergy, their relevance to various clinical manifestations is often uncertain.^{4,5} The presence of sIgE alone (sensitization) does not necessarily imply the existence of allergic symptoms, and indeed, there is a number of individuals who are sensitized but who are not clinically allergic.⁶ Likewise, in a subgroup of patients with a typical history suggestive of allergy, these tests are negative. Because local reaction to allergens in the nose is not measured, SPT and sIgE may not be sufficient to differentiate between allergic, non-allergic, and local allergic rhinitis (LAR). Using SPT, we have performed an epidemiology study on the prevalence of sensitization in patients with rhinitis in mainland China and found house dust mite (HDM) to be the most prevalent allergen.⁷ However, it turned out that skin sensitization to HDMs was not associated with the severity of allergic rhinitis.⁸ This seeming contradiction triggered our further investigation.

Nasal provocation testing aims at eliciting a nasal response by delivering specific allergens to the nose.⁹ The purpose of the allergen specific provocation is to reproduce the reaction occurring during the natural exposure to allergens. Thus, nasal allergen challenge allows demonstration of both the presence of allergen sIgE and the causal role of the allergen¹⁰ in nasal mucosal symptoms. In various guidelines, nasal provocation is now considered as the best available gold standard.¹¹

To our knowledge, few studies compare the associations of the SPT, serum sIgE, and nasal provocation testing with the severity of clinical symptoms. The aim of this study was to investigate the relationship between severity of allergic rhinitis and these 3 allergen diagnostic tests in patients sensitized to *Dermatophagoides pteronyssinus* (DP).

Material and Methods

Study Participants

Patients (aged 18–55 years) with ≥ 1 year history of rhinitis symptoms ($n = 65$), including 50 subjects with DP sensitization (DP+) and 15 subjects without DP sensitization (DP–), and healthy controls (HCs) ($n = 52$, including 15 with DP+ and 37 with DP–), were enrolled in the study. Rhinitis was defined as having symptoms of sneezing, or a running, itchy, or blocked nose when the

patient did not have a cold or flu. Inclusion criteria also included no regular use of any medication, no other additional chronic nasal diseases, and no use of antihistamines or steroid at least 2 weeks prior to this study. Exclusion criteria included a clinical history of asthma, smoking, allergy to pollens, molds or pets, and rhinitis caused by infection. Spirometry testing, including forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁), was performed to evaluate lower airway obstruction. The study was approved by the ethical committee of the first affiliated hospital of Guangzhou Medical University and we have obtained written informed consent from all subjects.

Assessment of Severity of Rhinitis

Severity of rhinitis was assessed with the validated Chinese translated version of Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), obtained from www.qoltech.co.uk/obtaining.html, which measures 28 functional (physical, emotional, and social) problems that are troublesome to rhinitis individual.¹² The subjects were asked to score the disturbance of each problem using a 7-point scale from 0 (not troubled) to 6 (extremely troubled). The mean score was then calculated by dividing sum score 168 with 28. The severity of rhinitis was graded from mild to severe symptoms according to the mean score categorized as follows: 0–0.44 = 0, 0.45–1.44 = 1, 1.45–2.44 = 2, 2.45–3.44 = 3, 3.45–4.44 = 4, 4.45–5.44 = 5, 5.45–6.0 = 6.

Skin Prick Test

The sensitivity to *Dermatophagoides* species (DP and *Dermatophagoides farinae*), cat, dog, *Blatella germanica*, *Alternaria alternata*, mixed grass, and mixed tree pollen allergen was tested. Allergen extracts and control solutions were obtained from ALK (Horsholm, Denmark). Histamine (10 mg/mL) and diluent were used as positive and negative controls. SPT was performed on the volar side of the forearm. The wheal reaction after 15 min was measured as the mean of the longest diameter and the length of the perpendicular line through its middle. A positive skin reaction was defined as a wheal size 3 mm greater than the negative control.

Blood Testing and Serum IgE Analysis

Peripheral blood was obtained from patients and HCs after completing the questionnaires and skin prick tests for eosinophil count and serum IgE measurements. Ten milliliters of blood from each subject was coagulated at room temperature, centrifuged, and stored at -20°C . Serum total IgE and sIgE against common allergens were measured by fluorescent enzyme immunoassay (Pharmacia CAP System, Pharmacia, Uppsala,

Sweden) as described previously.¹³ Serum samples were run in single determinations and evaluated against the stored calibration curve. The analysis for sIgE was defined to be positive if the measurement was ≥ 0.35 kU/L.

Nasal Provocation Test

Nasal Provocation Test (NPT) was performed according to guidelines of the German Society for Allergy and Clinical Immunology¹⁴ using a Rhino V-4.53 rhinomanometer (Jaeger, German). All diluent and DP solution were delivered toward the inferior turbinate with a nebulizer with a fixed volume of 100 μ L per puff. Solutions were applied to the subjects during breath holding after a deep inspiration to avoid allergen inhaled down to lower airways. Nasal airway resistance (NAR) was repeatedly measured at a transnasal pressure difference of 150 Pa with active rhinomanometry. Shortly after a 30-min adaptation period, the subjects were given 100 μ L of diluent to evaluate for nasal hyper-reactivity. In the absence of non-specific hyper-responsiveness, increasing concentrations of standardized DP allergen extract (100, 1000, 10 000, and 100 000 SQ-U/mL, Aquagen, ALK, Denmark) were then applied in both nostrils at 10-min intervals. After each application, clinical symptoms were determined and rhinomanometry performed. 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, throat) = 1; and conjunctivitis + cough + urticaria and/or dyspnea = 2.¹¹ NPT was considered positive if the total symptom score was ≥ 4 or nasal airflow at 150 Pa was reduced by $\geq 60\%$ of the baseline level. Challenge was also considered positive if nasal airflow was reduced $\geq 20\%$ with symptom score ≥ 3 . Nasal responsiveness was graded according to the dosage (SQ-U/mL) of DP allergen for NPT positivity being induced, using the following categories: 0: DP $> 100\,000$; 1: $10\,000 < \text{DP} \leq 100\,000$; 2: $1000 < \text{DP} \leq 10\,000$; 3: $100 < \text{DP} \leq 1000$; 4: $10 < \text{DP} \leq 100$; 5: diluent and DP ≤ 10 .

Visual Analogue Scales Assessment

A Visual Analogue Scale (VAS) was used for the quantitative evaluation of severity of allergic rhinitis symptoms according to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.^{15,16} VAS change has high sensitivity and specificity in diagnosing allergic rhinitis during nasal provocation test.¹⁷ Our subjects were asked to complete the VAS, which consist of a 10-cm long line on paper with markings at every 1 cm interval. Rhinorrhea, sneezing, itching, and congestion on the 0–10 cm scale were determined at baseline and after nasal challenge.

Statistical Analysis

SPSS version 16.0 was used for statistical analysis. Baseline characteristics that were quantitative parameters were presented as means and standard deviations. Total IgE, sIgE, VAS, and RQLQ scores were skewed distributions and expressed as medians with quartiles. The number of patients with NPT positivity and at the respective dose of DP-NPT were compared between groups by χ^2 analysis. Nasal resistance was assessed by the Wilcoxon paired test. VAS was assessed by the Mann–Whitney *U* test and the Kruskal–Wallis test with Dunn's multiple comparison test. Correlations between wheal size of skin test, level of sIgE, and dose of DP-NPT were analyzed by the Spearman's rank order test and linear regression analysis. Correlations between 3 allergen testing levels and severity of rhinitis were assessed by χ^2 analysis. All *P* values of $< .05$ were regarded as statistically significant.

Results

Participants

There were no significant differences between rhinitis and healthy controls in regards to gender distribution, age, percent predicted FEV₁ (FEV₁%), FEV₁/FVC ratio, and BMI. Rhinitis with DP+ had the highest blood eosinophil count and greatest DP skin wheal size, sIgE, and total IgE levels. Basal VAS scores and overall RQLQ scores were significantly higher in rhinitis with DP+, followed by rhinitis with DP–, when compared with healthy controls ($P < .01$, Table 1). In RQLQ detail categories, scores for sleep, practical problems, nasal symptoms, and eye symptoms were significantly higher in rhinitis with DP+, followed by rhinitis with DP–, when compared with healthy controls ($P < .01$, Table 1), while scores for activities, non-hay-fever symptoms, and emotions were higher in rhinitis with DP–, followed by rhinitis with DP+ ($P < .05$, Table 1), when compared with healthy controls ($P < .01$, Table 1).

Nasal Responsiveness to NPT

All the rhinitis subjects with DP+, 6 (40%) of the rhinitis subjects with DP–, and 2 (13.3%) of the healthy subjects had positive responses to NPT. None of the healthy subjects with negative SPT to DP had positive response to NPT. Regardless of the formal positivity of the NPT, NAR increased significantly in both rhinitis and healthy subjects after DP-NPT (all $P < .01$) with the highest in DP+ rhinitis group (Table 2).

Table 1. Baseline Characteristics of the Subjects.

	Rhinitis N = 65		Healthy Controls N = 52	
	DP+	DP–	DP+	DP–
Subjects (n)	50	15	15	37
Gender (M/F)	27/23	8/7	9/6	20/17
Age (years)	28.8 ± 6.7	30.1 ± 7.6	26.9 ± 6.5	28.6 ± 7.2
BMI (kg/m ²)	22.9 ± 2.5	23.3 ± 2.4	21.8 ± 2.1	22.8 ± 2.1
Blood eosinophils (× 10 ⁹ /L)	0.5 ± 0.3	0.19 ± 0.1	0.1 ± 0.1	0.1 ± 0.1 ^a
FEV ₁ /Pred (%)	96.7 ± 11.5	96.2 ± 13.2	100.4 ± 12.3	98.3 ± 9.4
FEV ₁ /FVC (%)	85.5 ± 8.7	84.7 ± 9.6	86.6 ± 6.0	88.1 ± 7.0
Wheal of DP SPT (mm)*	7.7 ± 2.4	0.0 ± 0.0 ^{a'}	3.4 ± 1.6 ^{a,b'}	0.0 ± 0.0 ^{a',c'}
Serum sIgE of DP (kU/L)*	38.8 ± 31.5	0.6 ± 0.5 ^{a'}	0.6 ± 0.6 ^{a'}	0.3 ± 0.5 ^{a'}
Total IgE (kU/L)*	317 ± 252	68 ± 52 ^{a'}	107 ± 66 ^{a',b'}	79 ± 76 ^{a',c'}
Basal VAS scores*	14.2 ± 10.0	6.4 ± 8.2 ^{a'}	1.0 ± 1.7 ^{a',b'}	1.3 ± 2.1 ^{a',b'}
Overall RQLQ scores*	64.4 ± 32.7	57.6 ± 38.5 ^{a'}	4.1 ± 3.2 ^{a',b'}	6.1 ± 5.2 ^{a',b'}
Activities*	5.4 ± 2.4	9.0 ± 6.4 ^a	0.4 ± 0.3 ^{a',b'}	0.5 ± 0.6 ^{a',b'}
Sleep*	8.5 ± 4.2	5.7 ± 4.6 ^{a'}	0.5 ± 0.3 ^{a',b'}	0.6 ± 0.5 ^{a',b'}
Non-hay-fever symptoms*	12.5 ± 8.4	16.6 ± 12.5 ^a	1.0 ± 0.8 ^{a',b'}	2.0 ± 1.7 ^{a',b'}
Practical problems*	10.2 ± 6.4	6.4 ± 5.3 ^{a'}	0.6 ± 0.5 ^{a',b'}	0.7 ± 0.8 ^{a',b'}
Nasal symptoms*	15.7 ± 7.8	9.9 ± 5.4 ^{a'}	1.2 ± 0.8 ^{a',b'}	1.7 ± 1.2 ^{a',b'}
Eye symptoms*	7.2 ± 5.2	1.1 ± 1.8 ^{a'}	0.4 ± 0.6 ^{a',b'}	0.2 ± 0.3 ^{a',b'}
Emotions*	6.0 ± 3.3	8.6 ± 7.7 ^a	0.0 ± 0.0 ^{a',b'}	0.0 ± 0.0 ^{a',b'}

Abbreviations: BMI, body mass index; DP, *Dermatophagoides pteronyssinus*; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; sIgE, specific immunoglobulin E; SPT, skin prick test; VAS, Visual Analogue Scales.

Data are expressed as mean ± SD or median ± interquartile range.

^a*P* < .05, ^{a'}*P* < .01, compared with rhinitis with DP+.

^b*P* < .05, ^{b'}*P* < .01, compared with rhinitis with DP–.

^c*P* < .05, ^{c'}*P* < .01, compared with healthy controls with DP+.

**P* < .01. Statistical significance was evaluated by Kruskal–Wallis test. Mann–Whitney *U* test was used to compare the differences between 2 groups when the result of Kruskal–Wallis test was significant.

VAS Scores

Baseline VAS scores, including rhinorrhea, sneezing, itching, and congestion, and total symptom score were found to be higher in rhinitis subjects with DP+, followed by rhinitis with DP–, when compared with healthy controls (all *P* < .05). After NPT, VAS scores increased in rhinitis subjects (all *P* < .05), while there were no significant differences in the healthy subjects (Table 2).

Correlation of Skin Wheal Size and Serum sIgE Blood Level With DP-NPT

Dose of DP inducing NPT response positively correlated with diameter of SPT for DP and the level of serum sIgE for DP in all tested subjects (*r* = .66, *P* < .001, and *r* = .52, *P* < .001, respectively, Figure 1).

Correlation Between Severity of Rhinitis, DP-NPT, Skin Wheal Size, and Serum sIgE in Rhinitis Patients

Scores of RQLQ positively correlated with dose of DP inducing NPT response (*P* < .001, Figure 2), but not with skin wheal size and level of serum sIgE for DP in

50 allergic rhinitis patients plus 6 local allergic rhinitis patients.

Discussion

In this study, we showed that responsiveness of nasal provocation testing was significantly associated with severity of the disease in overall DP-sensitized allergic rhinitis subjects. Although skin test and sIgE blood levels correlated well with dose of DP-NPT, they showed no association with the severity of rhinitis.

The severity of allergic rhinitis can be currently determined in ARIA with scores of RQLQ according to the degree of disturbance in quality of life. Several disease control questionnaires have been developed to assess the symptom severity of rhinitis,¹⁵ but there are few accurate and objective parameters to determine the disease severity. Some studies showed a poor correlation between nasal symptoms and inflammatory parameters, such as ICAM-1 and eosinophils in nasal mucosa.¹⁸ Although endoscopy appears to be a reliable tool to estimate the degree of subjective nasal symptoms,¹⁹ in this study we showed that the dosage of DP triggering a positive NPT

Table 2. Nasal Airway Resistance and VAS Symptom Scores at Baseline and After Challenge.

	Rhinitis N = 65		Healthy Controls N = 52	
	DP+	DP–	DP+	DP–
Subjects (n)	50	15	15	37
NPT positivity, n (%) ^a	50/50(100)	6/15(40)	2/15(13.3)	0/37(0)
Dose of DP-NPT (SQ-U/ml) ^a				
10	1	0	0	0
100	4	1	0	0
1000	11	0	0	0
10 000	17	3	1	0
100 000	17	2	1	0
>100 000	0	9	13	37
Basal NAR (Pa/cm ³ /s)	0.22±0.14	0.18±0.03	0.18±0.05	0.19±0.06
Positivity NAR (Pa/cm ³ /s)	0.43±0.28	0.27±0.08	0.24±0.11 ^{a'}	0.22±0.08 ^{a'b'}
P	.000	.001	.001	.001
Itching				
Baseline	2.2±1.8	0.5±1.3 ^{a'}	0.1±0.3 ^{a'b}	0.4±0.6 ^{a'}
Positivity	3.8±2.3	0.7±1.4 ^{a'}	0.4±0.7 ^{a'b}	0.5±0.8 ^{a'b}
P	.021	.026	NS	NS
Sneezing				
Baseline	2.3±2.4	0.2±0.6 ^{a'}	0.3±1.0 ^{a'}	0.2±0.4 ^{a'}
Positivity	4.3±3.9	0.4±1.1 ^{a'}	0.3±0.7 ^{a'b}	0.3±0.5 ^{a'b}
P	.028	.034	NS	NS
Rhinorrhea				
Baseline	1.9±1.8	0.5±1.3 ^{a'}	0.1±0.5 ^{a'b}	0.2±0.6 ^{a'b}
Positivity	4.2±3.3	2.6±1.8 ^{a'}	0.4±0.7 ^{a'b}	0.3±0.5 ^{a'b}
P	.018	.008	NS	NS
Congestion				
Baseline	1.8±2.0	0.7±1.2 ^{a'}	0.4±0.7 ^{a'b}	0.3±0.7 ^{a'b}
Positivity	4.2±3.7	2.8±2.7 ^{a'}	0.7±1.0 ^{a'b'}	0.5±0.8 ^{a'b'}
P	.028	.001	NS	NS
Total VAS				
Baseline	8.3±10.2	2.0±2.5 ^{a'}	0.9±1.5 ^{a'b'}	1.2±2.5 ^{a'b'}
Positivity	16.8±12.4	4.9±4.2 ^{a'}	1.6±2.2 ^{a'b'}	1.7±2.3 ^{a'b'}
P	.001	.001	NS	NS

Abbreviations: DP, *Dermatophagoides pteronyssinus*; NAR, nasal airway resistance; NS, non-significant; NPT, nasal provocation test; VAS, visual analogue scale.

^aP<.05, ^{a'}P<.01, compared with rhinitis with DP+.

^bP<.05, ^{b'}P<.01, compared with rhinitis with DP–.

^cP<.05, ^{c'}P<.01, compared with healthy controls with DP+.

*NPT positivity and number of subjects were compared between groups by χ^2 analysis with P<.01. NAR and VAS symptom scores are expressed as mean ± SD. NAR was evaluated by Mann–Whitney U test and VAS symptom scores by Kruskal–Wallis test.

provides a good noninvasive parameter to evaluate the severity of allergic rhinitis accurately.

Despite numerous epidemiological studies, the links between atopy, allergens, sensitization, and allergic rhinitis remain difficult to evaluate and are still incompletely understood.²⁰ SPT and blood sIgE are in vivo and in vitro tests that reflect the systemic allergic response.²¹ Although skin prick test is a sensitive method in discriminating subjects with or without AR,²² especially to the common inhalant allergens such as pollens and mites, skin testing correlates less well with the severity of illness.²³ Explanations for these findings might include

that the skin is not the primary organ involved in aero-allergen diseases, and that NPT can increase histamine in early phase and eosinophil cationic protein (ECP) in late phase,²⁴ whereas SPT only reflects the early phase response. Furthermore, both SPT and measurement of blood sIgE demonstrate the presence of systemic immune response, while NPT allows demonstration not only of the causal role of allergen but also the local production of allergen sIgE in the nasal mucosa.

Allergic rhinitis symptoms are result from a complex, allergen-driven mucosal immunologic response, modulated by IgE. Increased levels of IgE and positive

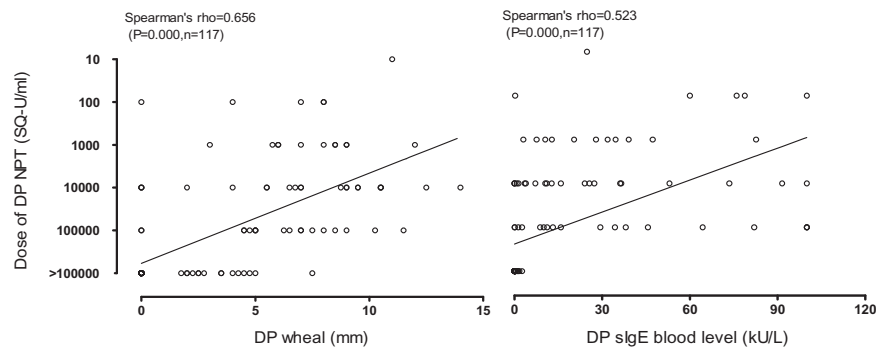


Figure 1. Correlation between dose of DP-NPT and wheal of SPT as well as level of serum sIgE.

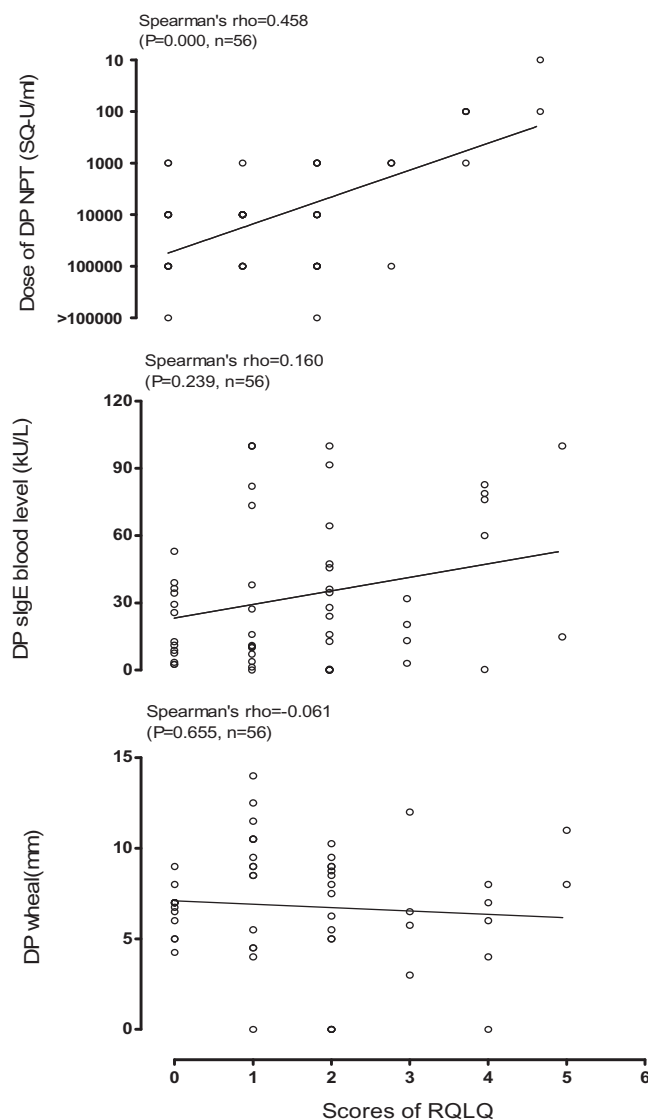


Figure 2. Correlation between severity of rhinitis, dose of DP-NPT, wheal of SPT, and level of serum sIgE in rhinitis patients.

reactivity on nasal allergen provocation tests have been demonstrated in nasal lavage fluid of patients with negative systemic allergy testing.²⁵ Interestingly, we found that 6 (40%) of the rhinitis patients without DP sensitization had positive response to DP-NPT, but conversely most of the healthy subjects with DP sensitization did not have positive response to NPT. Those 6 patients could be diagnosed as LAR, perhaps with DP specific localized IgE in these patients, although we did not measure nasal IgE in this study. Of note is that NPT would be a useful tool for the diagnosis of LAR.²⁶

NPT can stimulate the immune response through 2 main routes: the IgE-dependent immediate response driven by allergen-IgE mediated mast cell, and the inflammatory late-phase response mediated by cytokines, such as IL-4, IL-5, and IL-13.²⁷ These cytokines induce IgE production in activated B cells. There is also a close relationship between localized IgE and nasal inflammatory cytokines, such as ECP, IL-8, and VEGF.^{25,27} Nasal mucosa is an organ affected intermittently or persistently by environmental aeroallergen. The effect of pollen challenge and environmental pollen exposure has been demonstrated.²⁸ There are also evidences support the chronic airway inflammation and structural remodeling elicited by continuous exposure to house dust mite in the mice model.²⁹ Therefore, we speculate that the patients who had moderate to severe rhinitis might be continuously exposed to house dust mite allergens in daily life, that might lead to continuous production of DP-specific localized IgE and continuous maintenance of allergic inflammation in the nose.

Although blood sIgE associated with AR symptom severity has been observed in some studies,³⁰ much of the serum sIgE might come from the IgE which spilled over into the circulation from nasal tissue,³¹ so nasal sIgE elucidated by NPT would be expected to have a closer relationship with allergic symptoms than would the blood sIgE levels.

There are associations among skin prick test, serum sIgE, and nasal challenge in mite allergy.³² Although the non-atopic controls gives a lot more statistical power to the correlation, our study showed a significant correlation for SPT and serum sIgE, with the dose of DP-NPT. It suggested that SPT and sIgE were both effective screening tests for allergic nasal response. However, it is important to recognize that NPT and SPT are not in agreement in some cases because of nonspecific hyper-reactivity and localized allergy.³³ NPT is a valuable test to confirm the diagnosis of house dust mite allergy, especially when the wheal from the SPT is small.³⁴ No obvious side effects are found in our study. The main difficulty is to distinguish false-positive and false-negative reactions. Therefore, stopping use of antihistamines for at least 3 days before NPT and applying diluent at the first place to exclude nasal hyper-reactivity is of importance.

In conclusion, although DP nasal provocation, skin prick wheal size, and blood sIgE level correlate with each other, only the results of DP-NPT correlated with severity of nasal symptoms. NPT should be considered as a valuable tool in settings where it is necessary to confidently verify the clinical relevance of an allergen. NPT might be considered prior to initiating a multi-year long series of allergen immunotherapy when there is any uncertainty regarding whether the SPT or sIgE documented sensitization is playing a causative role in symptomatology. Further studies will be required to elaborate the complicated associations of environmental house dust mite exposure with responsiveness of DP challenge and symptom severity in AR patients.

Declaration of Conflicting Interests

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

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