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Evaluation of the Nasal Provocation Test for Its Necessity in the Diagnosis of Nasal Allergy to House Dust Mite

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SUMMARY The aim of this study was to evaluate rhinomanometric responses to nasal allergen provocation in children with allergic rhinitis sensitized to house dust mite. We studied 51 children, aged 6-16 years (mean: 11.5 ± 2.6 years), with clinical symptoms of perennial allergic rhinitis without asthma and 20 non-atopic healthy controls in the same age range (mean: 11.8 ± 3.8 years). All of the patients had positive skin prick test (SPT) results and serum specific IgE above 0.70 kU/l to *Dermatophagoides pteronyssinus* (*Dp*). Nasal provocation testing (NPT) was performed with increasing concentrations of *Dp* extracts and the nasal response was evaluated by active anterior rhinomanometry. A 100% increase of resistance in one or both nasal cavities was considered positive. There was a statistically significant difference of baseline nasal resistance (total, right and left sides) between the control and the patient groups ($p < 0.001$). A positive response to house dust mite allergens was recorded in 47/51 (92.2%) patients by rhinomanometry. The NPT presented no significant correlation with age, weight, height, SPT diameter, serum total and specific IgE levels to *Dp* and baseline nasal airway resistance values. This study suggests that a nasal provocation test with allergen is unnecessary in children with positive skin prick test and serum IgE specific to house dust mite. The rhinomanometric response to the allergen provocation does not correlate with the diameter of the skin prick test and the level of serum specific IgE.

Allergic rhinitis is the most common allergic condition in childhood. An accurate diagnosis and a well-planned therapy of allergic rhinitis are important, as this knowledge could significantly alter the social life of the patients as well as their school performance and cognitive functions.

A diagnosis of allergic rhinitis is especially difficult when no symptoms are expressed. It is essential to make the correct diagnosis with the appropriate tests while minimizing unnecessary testing. Skin tests and tests to measure serum specific IgE are the most commonly used diagnostic methods for allergic rhinitis, but sensitivities and specificities of these tests vary widely. The results of studies performed to determine the diagnostic value and precision of the quantitative skin test, RAST and specific nasal provocation tests (NPT) have suggested using standardized provocation tests in order to restrict diagnosis to the truly causative allergens in patients with positive skin prick test (SPT) results.[1]

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Intranasal allergen challenges have been used to study the pathogenesis of disease expression, to evaluate the efficacy of therapies and to diagnose the allergic status.[2-4] In patients with multiple sensitivity reactions, a specific NPT can identify the allergen presumably responsible for the nasal reactions.[5]

Specific-allergen immunotherapy is a useful and important treatment for many patients with severe allergic rhinitis.[6,7] Although immunotherapy has been demonstrated to be effective for allergic rhinitis and allergic asthma, an appropriate patient selection is imperative.

Immunotherapy should be considered for the treatment of allergic rhinitis in patients with evidence of clinically relevant allergen-specific IgE, significant symptoms despite reasonable allergen avoidance measures and already receiving maximal medical therapy. At this point, the most important step is to document the clinical effects of specific-allergen exposure in the nose.

Rhinomanometry is frequently used to assess nasal airway ventilation in clinical practice. The International Committee on Objective Assessment of the Nasal Airway recommends rhinomanometry as one of the methods of evaluating nasal response to NPT.[8] In active anterior rhinomanometry (AAR) the nasal flow is measured from one nasal cavity and the pressure gradient from the other during tidal breathing.[9]

The majority of children with allergic rhinitis are sensitized to house dust mites. Identifying house dust mite allergen as the cause of the symptoms and setting up a rational immunotherapy is especially difficult in the pediatric age group. The aim of this study was to assess nasal allergy with a specific NPT in a group of children with allergic rhinitis, who were homogenously allergic to house dust mites (shown with SPT and serum IgE levels).

In the present study, we report the results of a NPT with *Dermatophagoides pteronyssinus* (*Dp*). We have measured the changes in nasal airway resistance (NAR) by AAR and determined its relation to the SPT diameter, serum total and specific IgE levels to *Dp* and baseline NAR values.

MATERIALS AND METHODS

Patient selection

We studied 51 children, aged 6-16 years (mean: 11.5 ± 2.6 years), with clinical symptoms of perennial allergic rhinitis without asthma and 20 non-atopic healthy controls in the same age range (mean: 11.8 ± 3.8 years). Patients with a positive SPT to lyophilized extracts of *Dp* (Laboratoire des Stallergenes, France) and high serum concentrations of total IgE as well as specific IgE to *Dp* (Unicap, Pharmacia and Upjon, Uppsala, Sweden) were selected for the study. Eosinophil percentage (%) in the nasal smear and pulmonary function testing by spirometry (Model 2600, Sensor Medics, CA, USA) were performed. The patients had not received any medication during the last two weeks and none of them had acute nasal symptoms or a history of asthma. Informed consent was obtained from the parents and the study was approved by the Ethics Committee of our institution.

Nasal provocation tests and measurement of nasal airway resistance

NAR values of total, right and left sides in both patients and controls were measured initially with AAR (Flowhandy Zan 100, Germany) for a baseline value following the guidelines of the International Committee for the Standardization of Rhinomanometry (ICSR).[10] After the first recording of NAR, 0.1 ml of the control substance (phosphate-buffered saline) was applied to each nostril to exclude patients with hyperactive nasal mucosa. A 100% increase of resistance of one or both nasal cavities was considered a positive response. If there were not significant changes of NAR measurements, then 0.1 ml of the allergen extract composed of 100% *Dp* (Laboratoire des Stallergenes, France) was delivered into each nostril by an atomizer in increasing concentrations. During the allergen application the patient held his/her breath and thereafter a nose clip was applied immediately to prevent inhalation into the larynx or lower airways. At first, 0.2 IR (Index of Biological Reactivity) *Dp* were applied. If the rhinomanometry measurements recorded no response, 1.2 IR *Dp* and 3.2 IR *Dp* were applied consecutively. Following the challenge, the patients were rested for 15 minutes each time and NAR val-

ues of the right and left cavities were calculated separately from the flow at a transnasal pressure of 150 Pascal (Pa) during quiet breathing with closed mouth by using AAR expressed in $Pa/cm^3/s$.

Statistical methods

The SPSS 12.0 for Windows Base was used for the analysis. The Mann-Whitney U test was used for the comparisons and the Pearson test for the correlations. Results were given as mean ± standard deviation.

RESULTS

The baseline characteristics of the studied subjects are summarized in Table 1. There was a statistically significant difference of baseline nasal resistance (total, right and left sides) between the control and the patient groups ($p < 0.001$) (Table 2). Baseline NAR values in controls and patients and NAR values in patients following NPT are given in Table 2.

All patients tested negative to saline. Nasal hyperreactivity to *Dp* was recorded in 47/51 (92.2%) patients by rhinomanometry. Four (7.8%) patients showed no significant changes by rhinomanometry after the final concentration of 3.2 IR *Dp*. Twenty-one (41.2%) patients were provoked by 0.2 IR, 20 (39.2%) patients by 1.2 IR and 6 (11.8%) patients by 3.2 IR (Table 2).

The NPT presented no significant correlation with the patients' age, gender, weight, height, nasal eosinophil percentage (%), SPT diameter, serum total and specific IgE levels to *Dp*, baseline pulmonary function tests or baseline NAR values.

DISCUSSION

We assessed the nasal response to NPT with *Dp* in children with perennial allergic rhinitis and found that the NPT evaluated by rhinomanometry had a high positivity in children sensitized to house dust mites. Nasal hyperreactivity to house dust mite allergens was recorded in 47/51 (92.2%) patients.

Nasal ventilation can be evaluated by rhinomanometry which measures the pressure and flow inside the nasal cavity. In a recent study, NAR was found to be significantly higher in patients with nasal disease compared to healthy controls.[11] In the present study, the mean total NAR was also found significantly higher in children with allergic rhinitis compared to normal subjects.

NPT with histamine is a reproducible way of evaluating nasal reactivity, but specific NPT has restricted indications.[12] NPT may be used to investigate the role of allergens implicated by history when allergy skin tests or tests for serum specific IgE are

Table 1 Characteristics of patients (n = 51) (mean ± SD*)

Age (years)	11.50 ± 2.57
Weight (kg)	39.52 ± 10.82
Height (cm)	147.88 ± 16.25
Sex (F/M)	19/32
Nasal eosinophils (%)	19.90 ± 15.68
FEV1 (% predicted)	95.50 ± 13.84
PEF (% predicted)	90.25 ± 11.46
FEF25-75 (% predicted)	110.76 ± 17.62
SPT (*Dp*) (mm)	5.20 ± 2.57
Total IgE (kU/l)	439.38 ± 423.58
Specific IgE (*Dp*) (kU/l)	34.53 ± 41.55

*SD: standard deviation

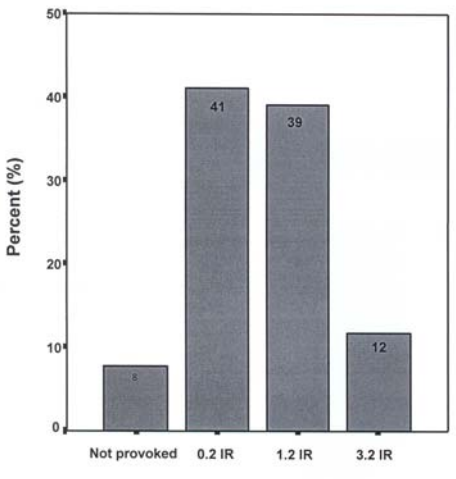

Fig. 1 The distribution of nasal provocation responses in patients.

Table 2 Baseline NAR values in controls and patients and NAR values in patients following nasal provocations (mean ± SD*)

Pa/cm^3/s	Control baseline N = 20	Patients					
		Baseline N = 51	Saline N = 51	0.2 IR *Dp* N = 21	1.2 IR *Dp* N = 20	3.2 IR *Dp* N = 6	No provocation N = 4
NAR total	0.32 ± 0.08	0.59 ± 0.26	0.60 ± 0.36	0.95 ± 0.60	1.29 ± 0.71	1.36 ± 0.80	0.67 ± 0.21
NAR right	0.63 ± 0.22	1.30 ± 1.04	0.97 ± 0.13	2.39 ± 2.37	3.76 ± 3.04	2.64 ± 1.73	1.68 ± 1.23
NAR left	0.68 ± 0.22	1.79 ± 1.58	1.56 ± 0.21	2.92 ± 3.18	2.94 ± 2.21	3.46 ± 2.31	4.90 ± 7.77

*SD: standard deviation
Baseline nasal resistances (total, right and left sides) were significantly different between the control and the patient groups ($p < 0.001$)

negative or give borderline results.[13,14] Some authors consider NPT as a gold standard in diagnosing allergy.[15,16] Nasal provocation with the suspected allergen confirms the diagnosis, but lack of standardization and monitoring methods have reduced its clinical value.[14,17]

Skin testing and measurement of serum specific IgE are generally used to diagnose allergic rhinitis.[18] Allergy skin tests are safe, sensitive, cheap and less time consuming diagnostic methods. The measurement of serum specific IgE also constitutes a safe technique of evaluating allergens especially in young children. If the SPT or a test for the specific IgE shows a positive reaction, a relationship between the allergen and the symptoms can be assumed. In some studies, a poor correlation was found between the diagnosis of allergic rhinitis and the results of SPT and specific IgE.[19,20] Nevertheless, some authors found a positive correlation between SPT and nasal challenge with mite allergens.[3,21] It was suggested that NPT was more specific than SPT in patients with allergic rhinitis.[21] Severity of symptoms, clinical history, SPT and allergen specific IgE levels were determined to be unreliable predictors in patients with chronic rhinitis unless confirmed with NPT.[22] It was also reported that only 4+ skin test positivity was associated with increased nasal reactivity to *Dp* and NPT was a useful test among the patients with allergic rhinitis.[23] In our study, NPT presented no significant relationship with SPT diameter and the degree of positivity for specific IgE levels to *Dp*.

A significant correlation was demonstrated between skin test and serum RAST and NPT to pollen, depending on the type of allergen tested.[24,25] In the case of moulds, NPT presented low correlations with the SPT and specific IgE levels.[26]

In one study, NPT with *D. farinae* was found positive in 63% of the patients and NPT with *Dp* in 62% by rhinomanometry.[21] Other studies determined higher positivity rates to NPT with *Dp* by rhinomanometry.[12, 27-30] We also found a high rate of positive (92.2%) responses to NPT by rhinomanometry in our patients with homogenously positive reactions to SPT and high specific IgE levels to house dust mites. This finding may imply that SPT and specific IgE positivity together with nasal symptoms can provide sufficient data to make a correct diagnosis.

Our study demonstrates that the rhinomanometric results after allergen provocation did not correlate significantly with the diameter of the SPT and the level of serum specific IgE. In conclusion, we suggest that a specific NPT, which takes relatively long time to perform, is not necessary for the diagnosis of allergic rhinitis in children with a positive SPT and high serum specific IgE levels to house dust mites.

REFERENCES

1. Pasterollo EA, Codecasal LR, Pravettoni V, *et al.* Clinical reliability of diagnostic tests in allergic rhinoconjunctivitis. Boll Ist Sieroter Milan 1988; 67: 377-85.
2. Doyle WJ, Skoner DP, Seroky T, Fireman P. Reproducibility of the effects of intranasal ragweed challenges in allergic subjects. Ann Allergy Asthma Immunol 1995; 74: 171-6.
3. Fernandes FR, Sole D, Naspitz C, Monoz-Lopez F. Diagnostic value of nasal provocation testing and rhinomanometry in allergic rhinitis. J Invest Allergol Clin Immunol 1996; 6: 184-8.

4. Kanthawatana S, Maturim W, Fooanant S, Manorot M, Trakultivakorn M. Evaluation of threshold criteria for the nasal histamine challenge test in perennial allergic rhinitis. Asian Pac J Allergy Immunol 1997; 15: 65-9.
5. Salzano FA. Specific nasal provocation test with powder allergen. Allergy 1997; 52: 32-5.
6. Varney VA, Jacobson MR, Sudderick RM, *et al.* Immunohistology of the nasal mucosa following allergen-induced rhinitis: identification of activated T lymphocytes, eosinophils and neutrophils. Am Rev Respir Dis 1992; 146: 170-6.
7. Leung DYM. Upper airway disease. In: Leung DY, Sampson HA, Geha RS, Szefler SJ. Eds. Pediatric Allergy: Principles and Practice, Mosby, USA, 2003; pp. 287-98.
8. Malm L, Gerth van Wijk R, Bachert C. Guidelines for nasal provocations with aspects on nasal patency, airflow, and resistance. International Committee on Objective Assessment of the Nasal Airways, International Rhinologic Society. Rhinology 2000; 38: 1-6.
9. Zapletal A, Chalupova J. Nasal airflow and resistance measured by active anterior rhinomanometry in healthy children and adolescents. Pediatr Pulmonol 2002; 33: 174-80.
10. Clement PAR. Committee report on standardization of rhinomanometry. Rhinology 1984; 22: 151-5.
11. Suzina AH, Hamzah M, Samsudin AR. Objective assessment of nasal resistance in patients with nasal disease. J Laryngol Otol 2003; 117: 609-13.
12. Barreto BA, Daher S, Naspitz CK, Sole D. Specific and nonspecific nasal provocation tests in children with perennial allergic rhinitis. Allergol Immunopathol 2001; 29: 255-63.
13. Litvyakova LI, Baraniuk JN. Nasal provocation testing: a review. Ann Allergy Asthma Immunol 2001; 86: 355-65.
14. Testa B, Mesolella C, Testa F, *et al.* Comparison of SPT and NPT in the ascertainment of nasal mucosa as shock organ. Rhinology 1996; 34: 160-2.
15. Eriksson NE, Ahlstedt S, Belin L. Diagnosis of reaginic allergy with house dust, animal dander and polen allergens in adult patients. I. A comparison between RAST, skin tests and provocation tests. Int Arch Allergy Appl Immunol 1976; 52: 335-46.
16. Carney AS, Powe DG, Huskisson RS, Jones NS. Atypical nasal challenges in patients with idiopathic rhinitis: more evidence for the existence of allergy in the absence of atopy? Clin Exp Allergy 2002; 32: 1436-40.
17. Melillo G, Bonini S, Cocco G, *et al.* Provocation tests with allergens. Allergy 1997; 52(Suppl): 5-36.
18. Daele J, Melon J. Skin tests, IgE, RAST and nasal provocation test. Acta Oto-Rhinolaryngol 1979; 33: 572-81.
19. Ng MLS, Warlow RS, Chrishanthan N, *et al.* Preliminary criteria for the definition of allergic rhinitis: a systematic evaluation of clinical parameters in a disease cohort (II). Clin Exp Allergy 2000; 30: 1417-22.
20. Stenius B. Skin and provocation tests with *Dermatophagoides pteronyssinus* in allergic rhinitis. Comparison of prick and intracutaneous skin test methods and correlation with specific IgE. Acta Allergol 1973; 28: 81-100.
21. Damps I, Mincewicz G, Polawska K, *et al*. Nasal provocation tests with house dust mite in patients with perennial rhinitis. Otolaryngol Pol 2003; 57: 69-74.
22. Riechelmann H, Mewes T, Weschta M, Gropper G. Nasal allergen provocation with *Dermatophagoides pteronyssinus* in patients with chronic rhinitis referred to a rhinologic surgical center. Ann Allergy Asthma Immunol 2002; 88: 624-31.
23. Kanthawatana S, Maturium W, Fooanan S, Trakultivakorn M. Skin prick reaction and nasal provocation response in diagnosis of nasal allergy to the house dust mite. Ann Allergy Asthma Immunol 1997; 79: 427-30.
24. Bousquet J, Lebel B, Dhivert H, *et al*. Nasal challenge with pollen grains, skin prick tests and specific IgE in patients with grain pollen allergy. Clin Allergy 1987; 17: 529-36.
25. Schumacher MJ, Pain MCF. Nasal challenge testing in grass pollen hay fever. J Allergy Clin Immnol 1979; 64: 202-8.
26. Modrzynski M, Zawisza E. Specific nasal provocation tests in patients hypersensitive to mould allergens. Med Sci Monit 2004; 11: 44-8.
27. Clarke PS. The diagnosis of perennial rhinitis due to house dust mite (*Dermatophagoides pteronyssinus*) demonstrated by nasal provocation tests. Ann Allergy 1987; 59: 25-8.
28. Olive Perez A. Nasal provocation test (NPT) through previously active rhinomanometry: physical and mathematical reasons. Allergol Immunopathol 1989; 17: 291-9.
29. Dokic D, Jovanovic S, Berghaus A, Brunnee T. Diagnosis of nasal allergy to house dust mite. Rhinology 1991; 29: 117-23.
30. Braga CR, Rizzo MC, Naspitz CK, Sole D. Nasal provocation test (NPT) with isolated and associated *Dermatophagoides pteronyssinus* (Dp) and endotoxin lipopolysaccharide (LPS) in children with allergic rhinitis (AR) and nonallergic controls. J Invest Allergol Clin Immunol 2004; 14: 142-8.