

The importance of measuring nasal IgE in children and adults with rhinitis and negative skin tests

Importanza della ricerca di IgE nasali in pazienti adulti e pediatrici con rinite e cutireazioni negative

N. FUIANO, C. INCORVAIA*

Pediatric Allergy Service, AUSL FG1, San Severo, Italy; * Allergy/Rheumatology, ICP Hospital, Milan, Italy

Key words

Rhinitis • Allergens • Pollens • Dust mites • Skin prick tests • Nasal IgE • Local production

Parole chiave

Rinite • Allergeni • Pollini • Acari della polvere • Test cutanei • IgE nasali • Produzione locale

Summary

Background

Rhinitis is a common disease, frequently caused by allergy. However, skin prick tests (SPT) and *in vitro* IgE tests not rarely provide negative results, leading to a diagnosis of nonallergic rhinitis; still, the possibility of a local nasal production of specific IgE cannot be excluded.

Methods

We measured specific nasal IgE in 125 subjects (63 males and 62 females, age ranging from 3 to 47 years) who had been referred to our Allergy centre for rhinitis. All subjects underwent SPT with a standard panel of aeroallergens during their examination. Statistical associations between a positive IgE nasal test result and clinical parameters were investigated.

Results

SPT were positive in 74 subjects (59.2%), with an overall number of 123 positive results: 38 to grass pollen, 34 to *Dermatophagoides*, 23 to *Oleaceae* pollen, 10 to *Parietaria* pollen, 9 to other pollens, 5 to cat epithelium, and 4 to *Alternaria*. Nasal IgE were positive in 82 subjects (65.6%), with an overall number of 124 positive results: 32 to *Oleaceae* pollen, 25 to *Parietaria* pollen, 19 to *Alternaria*, 12 to grass pollen, 11 to *Dermatophagoides*, 9 to cat epithelium, 9 to birch pollen, and 7 to other pollens. In 16 subjects only nasal IgEs were positive. A significant association was found between a positive result from the nasal test and current symptoms in children.

Conclusions

These data indicate that in subjects with rhinitis and negative SPT measuring nasal IgE during the symptomatic period may reveal a local production of specific IgE demonstrating the allergic nature of symptoms.

Riassunto

Introduzione

La rinite è un'affezione comune, spesso causata da allergia. Tuttavia, non raramente i test allergologici cutanei o *in vitro* danno un risultato negativo, suggerendo una diagnosi di rinite non allergica; in questi casi si deve tenere presente la possibilità di una produzione di IgE solo locale a livello della mucosa nasale.

Metodi

Abbiamo misurato le IgE specifiche nasali in 125 pazienti (63 maschi e 62 femmine, di età tra 3 e 47 anni) presentatisi al nostro Servizio allergologico per rinite. In tutti i pazienti sono stati eseguiti test cutanei con un pannello standard per allergeni inalanti. Sono state analizzate le associazioni statistiche tra positività dei test nasale e cutaneo e parametri clinici.

Risultati

I test cutanei sono risultati positivi in 74 soggetti (59,2%), con un numero complessivo di 123 positività: 38 a polline di graminacee, 34 a *Dermatophagoides*, 23 a polline di *Oleaceae*, 10 a polline di *Parietaria*, 9 a altri pollini, 5 a epitelio di gatto e 4 ad *Alternaria*. Il test per IgE nasali è risultato positivo in 82 soggetti (65,6%), con un numero complessivo di 124 positività: 32 a polline di *Oleaceae*, 25 a polline di *Parietaria*, 19 ad *Alternaria*, 12 a polline di graminacee, 11 a *Dermatophagoides*, 9 a epitelio di gatto, 9 a polline di betulla e 7 ad altri pollini. In 16 soggetti solo il test nasale ha dato esito positivo. È stata riscontrata un'associazione significativa tra positività del test nasale e sintomi in atto.

Conclusioni

Questi dati indicano che in soggetti con rinite e cutireazioni negative la misurazione delle IgE nasali nel periodo sintomatico può rivelare una produzione locale di IgE specifiche che dimostra la natura allergica dei sintomi.

Introduction

The detection of IgE antibodies to environmental allergens by means of skin tests or *in vitro* tests indicates sensitization but not necessarily clinical allergy¹. In fact, in epidemiological studies the prevalence of sensitization is much higher – reaching 40% of the investigated subjects – than the prevalence of symptomatic allergy, currently estimated at 10-25%²⁻⁵. By contrast, in patients with clinical symptoms of rhinitis and rhinoconjunctivitis skin tests and *in vitro* tests may not rarely give a negative result, which can lead to a diagnosis of nonallergic disease.

It has been long suggested that these subjects may have an exclusive local production of IgE, which once demonstrated by appropriate *in vitro* techniques⁶⁻⁸ results in a correct diagnosis of allergy.

In a group of patients with nose and eye symptoms we performed skin prick tests using a standard panel of aeroallergens and nasal IgE measurement to the same allergens employing a validated technique, and investigated the factors possibly able to influence a positive response.

Material and methods

PATIENTS

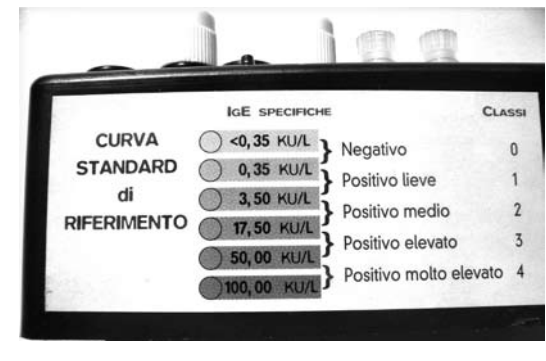
The subjects for this study were taken from patients consecutively referred to our Allergy centre for rhinitis or rhinoconjunctivitis. In total 125 subjects (63 males and 62 females, mean age 16.6 years, with an age range of 3-47 years) were included in the study. The patients were divided into two groups according to whether they were children/adolescents (age ≤ 18 years of age, group A) or adults (age > 18 years of age, group B).

METHODS

Skin prick tests (SPT) were performed employing the standard technique⁹ using a panel of the aeroallergens commonly found in Italy, including grass, birch, cypress, ragweed, and *Parietaria* pollens, house dust mites, cat epithelium, and moulds (Stallergènes, Milan, Italy).

Nasal IgE were measured by the technique described by Marcucci et al.¹⁰, and named by the Authors nasal test (NT). In brief, the test involved placing the allergen-coupled cellulose derivative onto a two hole applicator strip covered with a permeable membrane (to avoid the adhesion of nasal mucus on the substrate) and then positioning it in the above-posterior tract of the internal ostium for 10 minutes. The results were subsequently read according to a colorimetric reaction as depicted in Figure 1. This material was supplied by Biomicon (Turin, Italy).

Fig. 1. Kit for measurement of nasal IgE.



STATISTICAL ANALYSIS

For the analysis each group was categorized according to age expressed as median: 9.8 years of age for group A and 30 years of age for group B.

The associations between the factors which could influence the response to SPT and nasal IgE measurement (gender, categorized age, presence or not of allergic symptoms at the time of testing, the season during which the tests were performed) were investigated by univariate analysis (Chi square test). Multivariate analysis (logistic regression) was used to evaluate the data in group A, since only in this group were detected significant associations by univariate analysis.

Results

Skin prick tests were positive in 74 subjects (59.2%), with an overall number of 123 positive results: 38 to grass pollen, 34 to *Dermatophagoides*, 23 to *Oleaceae* pollen, 10 to *Parietaria* pollen, 5 to cypress pollen, 5 to cat epithelium, 4 to *Alternaria*, 2 to ragweed, and 2 to birch. Nasal IgEs were positive in 82 subjects (65.6%), with an overall number of 124 positive results: 32 to *Oleaceae* pollen, 25 to *Parietaria* pollen, 19 to *Alternaria*, 12 to grass pollen, 11 to *Dermatophagoides*, 9 to cat epithelium, 9 to birch pollen, 5 to ragweed, and 2 to cypress. In 16 subjects (13%) only the nasal IgE test was positive. Table I reports all the positive tests according to the season in which they were conducted.

In group A (children) significant associations were found from the outcome of univariate analysis between a positive result to the nasal test and the current presence of symptoms ($p < 0.05$) and between a positive result to the skin prick tests. Whereas in the older age group (higher than the median of 9.8 years of age) no significant associations were detected from the results of multivariate analysis.

Tab. I. Results of SPT and NT according to the season during which the tests were performed.

	Spring		Summer		Autumn		Winter	
	SPT	NT	SPT	NT	SPT	NT	SPT	NT
Alternaria	2	2	0	2	1	9	1	6
Ragweed	1	1	0	0	1	3	0	1
Birch	0	1	0	0	1	5	1	3
Cypress	1	1	1	0	0	1	3	0
Dust mites (mix)	4	2	7	0	12	2	11	7
Cat epithelium	0	0	2	0	0	1	3	8
Grasses (mix)	3	1	4	3	15	6	16	2
Olive	4	1	3	8	5	11	11	12
Parietaria	1	3	1	2	3	7	5	13

Discussion

Allergic diseases are becoming increasingly prevalent making them the most common pathology, particularly in children²⁻⁴. Diagnosing allergy is relatively easy when the symptoms affecting the nose (such as sneezing, rhinorrhea, and nasal obstruction), the eye (such as itching, weeping, and redness) and the lungs (such as wheezing and coughing) correspond to a positive result from allergy tests. The most common forms of allergy test are the skin prick tests or *in vitro* tests of the RAST type, with the former taking a more prevalent role due to its readiness and convenience¹¹.

However, it is not uncommon that subjects with a clinical history which strongly suggests allergy do not demonstrate any sensitization to allergy testing. A number of false negative results may be explained by the fact that the subjects have not been tested using the relevant allergens, by the use of inappropriate material, and by errors in technique. Still, a substantial quota of such patients show negative results even when optimal material and technique has been used, thus suggesting that their symptoms are caused by a non allergic pathogenesis. Indeed, the possibility of an exclusively local production of allergen specific IgE antibodies should not be overlooked. This phenomenon was demonstrated thirty years ago⁶⁻⁸ and recently revised in its clinical aspects and immunologic background¹², but the search for local IgE is not yet considered in the diagnosis of patient with rhinitis when skin prick tests or *in vitro* tests are negative.

In a recent study the nasal IgE test, performed on 28 children with a history clearly suggesting allergy, showed a sensitivity of 78.6% compared to a sensitivity of 75% from the skin prick test, while the specificity was 98% and 83%, respectively¹³.

The results of the present study indicate that in a group of 125 patients with a mean age of 16 years suffering from rhinitis, nasal IgE are present in 65.6% of subjects compared with 59.2% of subjects showing skin IgE, thereby confirming the observations made by Marcucci et al.¹³. The rate of positive skin tests increased with age, in accordance with what we know from previous observations⁹. However, the most important finding is that in 13% of patients only the nasal IgEs were found, and this highlights the possibility of arriving at an incorrect diagnosis of non allergic rhinitis if the nasal test is not performed. The factor statistically associated with such a probability is the current presence of symptoms, suggesting that in some subjects the local production is triggered only during the exposure to the specific allergen. Some Authors proposed the term "entopy" to define the localized mucosal allergic disease without systemic response, which appears to be particularly frequent in pollen allergy¹⁴.

This kind of immune response should be borne in mind especially when a patient with seasonal rhinitis does not show positive results to skin prick tests or *in vitro* IgE tests, which suggests that the possibility of a nasal local production should be verified using the simple kit for nasal IgE.

References

- Pastorello EA, Incorvaia C, Ortolani C, Bonini S, Canonica GW, Romagnani S, et al. *Studies on the relationship between the level of specific IgE antibodies and the clinical expression of allergy. I. Definition of levels distinguishing patients with symptomatic from patients with asymptomatic allergy to common aeroallergens.* J Allergy Clin Immunol 1995;96:580-7.
- The International Study of Asthma and Allergies in Childhood (ISAAC). *Steering Committee. Worldwide variations in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and hay fever in children: the ISAAC study.* J Allergy Clin Immunol 1998;101:99-106.

-
- ctivitis, and atopic eczema. Lancet* 1998;351:1225-32.
- ³ Sestini P, De Sario M, Bugiani M, Bisanti L, Ciccone G, et al. *Frequency of asthma and allergies in Italian children and adolescents: results from SIDRIA-2. Epidemiol Prev* 2005;29:24-31.
 - ⁴ Galassi C, De Sario M, Biggeri A, Bisanti L, Chellini E, Ciccone G, et al. *Changes in prevalence of asthma and allergies among children and adolescents in Italy: 1994-2002. Pediatrics* 2006;117:34-42.
 - ⁵ Tepes EC, Litonjua AA, Celedon JC. *Sensitization to aeroallergens and airway hyperresponsiveness at 7 years of age. Chest* 2006;129:1500-8.
 - ⁶ Huggins K, Brostoff J. *Local production of specific IgE antibodies in allergic rhinitis patients with negative skin tests. Lancet* 1975;2:148-50.
 - ⁷ Merrett TG, Hourri M, Mayer ALR, Merrett J. *Measurement of specific IgE antibodies in nasal secretions. Evidence for local production. Clin Allergy* 1976;6:69-73.
 - ⁸ Deuschl H. *Immunoglobulins in nasal secretion with special reference to IgE. Int Arch Allergy Appl Immunol* 1976;52:376-83.
 - ⁹ Dreborg S. *Skin tests used in type I allergy testing. Position paper of the EAACI. Allergy* 1989;(Suppl 10):44.
 - ¹⁰ Marcucci F, Sensi L. *A new method of IgE detection in nasal mucosa. Clin Exp Allergy* 1989;19:157-62.
 - ¹¹ Host A, Andrae S, Charkin S, Diaz-Vázquez C, Dreborg S, Eigenmann PA, et al. *Allergy testing in children: why, who, when and how? Allergy* 2003;58:559-69.
 - ¹² Fokkens WJ, Vinke JG, Kleinjan A. *Local IgE production in the nasal mucosa: a review. Am J Rhinol* 2000;14:299-303.
 - ¹³ Marcucci F, Passalacqua G, Canonica GW, Frati F, Salvatori S, Di Cara G, et al. *Measurement of nasal IgE in an epidemiological study: assessment of its diagnostic value in respiratory allergy. Allergol Immunol* 2004;36:225-31.
 - ¹⁴ Powe DG, Jagger C, Kleinjan A, Carney AS, Jenkins D, Jones NS. *"Entropy": localized mucosal allergic disease in the absence of systemic responses for atopy. Clin Exp Allergy* 2003;33:1374-9.