ORIGINAL ARTICLE

Allergen-Specific Immunoglobulin E in the Skin and Nasal Mucosa of Symptomatic and Asymptomatic Children Sensitized to Aeroallergens

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Abstract

Background: Asymptomatic sensitization is confirmed by a positive response to skin prick tests (SPT) with allergens in the absence of clinical symptoms of allergy. This is a common observation for which no convincing explanation has been provided. We investigated the extent to which the presence of specific immunoglobulin (Ig) E in the nasal mucosa accounts for the occurrence of symptoms
Methods: The study population comprised 192 patients with positive SPT results to aeroallergens: 111 had symptomatic allergic rhinitis and 81 were totally asymptomatic. All patients underwent measurement of nasal specific IgE using a validated technique (nasal IgE test).
Results: A family history of atopy was significantly more frequent in symptomatic patients than in asymptomatic patients ($P<.0001$). The result of the nasal IgE test was positive in 77.5% of symptomatic patients and in only 13.6% of asymptomatic patients ($P<.0001$). With regard to individual allergens, there was no association between clinical symptoms and a positive response to SPT, although there was a strong association between symptoms and individual allergens tested for nasal IgE. In symptomatic patients, there was only a slight correlation between SPT and nasal tests with allergens.
Conclusion: These findings suggest that the absence of specific IgE in the nasal mucosa may explain the absence of symptoms in most sensitized subjects and pave the way for further study of the behavior of mucosal IgE in asymptomatic and symptomatic subjects.

Key words: IgE. Sensitization. Asymptomatic. Skin prick test. Nasal IgE.

Resumen

Antecedentes: La sensibilización asintomática se confirma mediante una respuesta positiva a pruebas de punción cutánea con alérgenos en ausencia de síntomas clínicos de alergia. Se trata de una observación frecuente para la que no se dispone de ninguna explicación convincente. En este estudio se investigó en qué medida la presencia de inmunoglobulina (Ig) E específica en la mucosa nasal está relacionada con la aparición de síntomas.
Métodos: La población en estudio incluyó a 192 pacientes con resultados positivos en las pruebas de punción para aeroalérgenos: 111 tenían rinitis alérgica sintomática y 81 eran totalmente asintomáticos. A todos los pacientes se les midió la IgE específica nasal utilizando una técnica validada (prueba de IgE nasal).
Resultados: Los antecedentes familiares de atopia fueron significativamente más frecuentes en los pacientes sintomáticos que en los asintomáticos ($p< 0,0001$). El resultado de la prueba de IgE nasal fue positivo en el 77,5% de los pacientes sintomáticos y solo en el 13,6% de los pacientes asintomáticos ($p< 0,0001$). En cuanto a los alérgenos individuales, no se observó ninguna asociación entre los síntomas clínicos y una respuesta positiva a la prueba de punción cutánea, si bien se observó una fuerte asociación entre los síntomas y los alérgenos individuales analizados para la IgE nasal. En los pacientes sintomáticos solo se registró una ligera correlación entre las pruebas de punción cutánea y las pruebas nasales con alérgenos.
Conclusión: Estos hallazgos indican que la ausencia de IgE específica en la mucosa nasal puede explicar la ausencia de síntomas en la mayoría de los individuos sensibilizados, y preparar el camino para futuros estudios sobre el comportamiento de la IgE de la mucosa en individuos sintomáticos y asintomáticos.

Palabras clave: IgE. Sensibilización. Asintomático. Prueba de punción cutánea. IgE nasal.

Introduction

Specific immunoglobulin (Ig) E antibodies to environmental allergens play a key role in respiratory allergy. However, although their presence—as assessed by skin tests or in vitro tests—indicates sensitization, it does not directly imply the occurrence of clinical allergy. In fact, many sensitized individuals have no symptoms of rhinitis or asthma [1]. This condition is known as asymptomatic sensitization. To date, no convincing explanation has been provided for this phenomenon, although some authors suggest that skin sensitization may be of prognostic value, since substantial numbers of sensitized individuals can develop clinical allergy, depending on the allergen and duration of follow-up [2]. Moreover, significantly higher levels of circulating specific IgE have been reported in symptomatic individuals [3]. Therefore, it is somewhat surprising that the role of specific mucosal IgE in the onset of symptoms has not been investigated. Specific IgE is found in the nasal mucosa of most patients with allergic rhinitis [4], and some of those with rhinitis and negative skin test results may have IgE only in the nasal mucosa, probably due to local production [5,6]. In contrast, the presence of specific IgE in the nose of asymptomatic individuals with a positive skin test result has never been evaluated. The fact that techniques for measurement of nasal IgE are not routinely available may account for this lack of data.

We used a validated technique to evaluate the presence of specific IgE in the nasal mucosa of symptomatic and asymptomatic sensitized children.

Material and Methods

Patients

The study population comprised consecutive patients with positive skin prick test (SPT) results to one or more aeroallergens. A detailed history was obtained from each patient. In addition, patients had to answer a standardized questionnaire covering the type of symptoms, occurrence, and age at onset [7,8]. Only symptoms that were definitely present or definitely absent were considered; suspected or uncertain symptoms were not taken into account.

The participants were divided in 2 groups. Group 1 comprised patients with symptomatic allergy. They all had a clear history of current rhinitis, with a well-defined association between the onset of allergic symptoms and exposure to the allergen(s) inducing a positive SPT result. Patients were excluded from the study if they had a history of rhinitis lasting more than 5 years (to avoid cases in which established inflammation might influence the patient's clinical status), if they had been treated with corticosteroids or other immunosuppressive therapy during the preceding 36 months, if they had an elevated IgE antibody level caused by another disease, or if they had ever received allergen immunotherapy. Group 2 comprised individuals with asymptomatic allergy. The inclusion criteria were a negative history of rhinitis and asthma caused by the allergens that elicited the positive SPT reaction, and the participants had been referred to our center for evaluation of symptoms caused by nonrespiratory allergens (eg, milk, egg, soy) or by other allergies, such as drug hypersensitivity. Special care was taken to exclude symptoms that might be caused by any of the 5 allergens included in this study. To be considered asymptomatic for pollens, patients must not have had respiratory symptoms during the corresponding pollen season. The exclusion criteria for this group were the same as for the symptomatic patients.

Skin Tests and Nasal IgE Test

All participants underwent SPT and measurement of specific IgE in the nasal mucosa, with the 5 most common allergens in our geographical area (grass, *Parietaria*, olive, house dust mite, and *Alternaria*). SPTs were carried out by the same investigator using standardized allergen extracts (Stallergènes, Antony, France) according to the position paper of the European Academy of Allergy and Clinical Immunology [9]. A wheal with a mean diameter ≥3 mm was considered positive [10].

The nasal IgE test was performed according to the technique described by Marcucci and Sensi [11] (Biomicron, Turin, Italy). In brief, the test involved placing the allergen-coupled cellulose derivative onto a 2-hole applicator strip covered with a permeable membrane (to avoid adhesion of nasal mucosa to the substrate) and then positioning the strip in the upper tract of the internal ostium for 10 minutes. The results were read as a colorimetric reaction and expressed on a scale of 0 (negative) to 4 (highly positive) using a calibration curve.

Statistical Analysis

Qualitative variables are expressed as a percentage and quantitative variables as mean (SD). Statistical analysis was performed using the χ^2 test for categorical variables and the *t* test for continuous variables. Contingency tables, the Pearson χ^2 test, and Fisher exact test were used to analyze the association between the categorical variables. Statistical significance was set at $P<.05$. The statistical analysis was performed using BMPD version 2007 (BMPD Statistical Software Inc., Los Angeles, California, USA).

Results

We studied 192 individuals (110 males; mean age, 9.5 [3.3] y [range, 3-15 y]). All patients had at least 1 positive SPT result, and 123 (64%) were sensitized to a single allergen. Ninety-seven patients (50%) had detectable nasal IgE, and 1 positive result was found in 63. All patients came from the same geographical area and were equally exposed to the allergens studied. According to the criteria set out above, 111 patients were symptomatic (64 males; mean age 9.1 [3.6] y [range, 3-15 y]) and 81 were asymptomatic (46 males; mean age 10 [2.9] y [range, 3-15 y]). Based on clinical history, 75 of the 111 symptomatic patients (67.6%) had a family history of atopy, compared with 28 of the 81 asymptomatic patients (34.6%). This difference was statistically significant ($P<.0001$). The most frequently positive allergens in symptomatic patients (according to SPT) were house dust mite, followed

by grass pollen and olive pollen, and 40.5% of patients were polysensitized. Similar rates were found among asymptomatic participants, where polysensitization was slightly less frequent. However, the rate of polysensitization assessed using the nasal IgE test was significantly higher in symptomatic than in asymptomatic participants (none were polysensitized according to SPT).

There was no statistical association between clinical symptoms and a positive response to SPT, whereas the association between symptoms and individual allergens by nasal IgE test was strong (Table 1). Furthermore, no association was found between SPT and nasal IgE test positivity in the sample as a whole or in symptomatic and asymptomatic participants.

Table 1. Association Between Symptoms and Results of the Skin Prick and Nasal Immunoglobulin E Tests

	Symptomatic (n=111)	Asymptomatic (n=81)	*P* Value
Male/Female	64/47	46/35	NS
Age, y, mean (SD)	9.1 (3.6)	10.0 (2.9)	NS
Positive SPT, No. (%)	111 (100)	81 (100)	
House dust mite	66 (59.5)	41 (50.6)	NS
Grass pollen	61 (54.9)	40 (49.4)	NS
Olive pollen	26 (23.4)	20 (24.7)	NS
Parietaria	10 (9.0)	3 (3.7)	NS
Alternaria	3 (2.7)	3 (3.7)	NS
Polysensitization, No. (%)	45 (40.5)	24 (29.6)	NS
Positive nasal IgE, No. (%)	86 (77.5)	11 (13.6)	<.0001
House dust mite	51	6	<.0001
Grass pollen	23	2	.0002
Olive pollen	12	0	.001
Parietaria	14	0	.0009
Alternaria	22	3	.0022
Polysensitization, No. (%)	52 (46.8)	0 (0.0)	<.0001

Abbreviations: Ig, immunoglobulin; NS, nonsignificant; SPT, skin prick test.

Table 2. Proportion of Positive Responses to the Skin Prick and Nasal Immunoglobulin E Tests for Each Allergen

	Symptomatic	Asymptomatic	*P* Value
Alternaria			
SPT	3	3	NS[a]
NT	22	3	
House dust mites			
SPT	66	41	.0002[b]
NT	51	6	
Grass pollen			
SPT	61	40	.003[a]
NT	23	2	
Olive pollen			
SPT	26	12	.005[b]
NT	20	0	
Parietaria			
SPT	10	14	NS[a]
NT	3	0	

Abbreviations: Ig, immunoglobulin; NS, nonsignificant; NT, nasal test; SPT, skin prick test.
[a]Fisher exact test
[b]Pearson χ^2 test

Table 3. Analysis of Reciprocal Positive or Negative Response to the Skin Prick and Nasal Immunoglobulin E Tests for Each Allergen

	IgE–/SPT– IgE+/SPT–	IgE–/SPT– IgE+/SPT+	*P* Value
Symptomatic			
Alternaria	86	3	
	22	0	NS
House dust mites	24	36	
	21	30	NS
Grass pollen	44	44	
	6	17	.04
Olive pollen	78	21	
	7	5	NS
Parietaria	78	21	
	7	5	NS
Asymptomatic			
Alternaria	74	4	
	3	0	NS
House dust mites	39	36	
	1	5	NS
Grass pollen	39	40	
	2	0	NS
Olive pollen	61	19	
	0	1	NS
Parietaria	77	4	
	0	0	NC

Abbreviations: Ig, immunoglobulin; NC, not computed; NS, nonsignificant; SPT, skin prick test.

The proportion of positive responses to SPT and nasal IgE test for individual allergens did not reveal an association for *Alternaria* and *Parietaria*, whereas an association was clearly present for house dust mite, grass, and olive (Table 2). Table 3 shows that, except for grass pollen, there was no association between the positive responses to the 2 tests for both symptomatic and asymptomatic subjects. When symptomatic patients were considered separately according to whether they were monosensitized or polysensitized, there was only a slight correlation between the 2 tests for the individual allergens.

Discussion

Since their discovery in 1967, IgE antibodies have been thoroughly investigated to determine their biological and clinical role in allergic diseases [12]. However, the factors underlying sensitization, as opposed to clinical expression, remain elusive. It has been confirmed that there are more asymptomatic than symptomatic individuals among those sensitized to common aeroallergens [13-15]. A recent document by the Global Allergy and Asthma European Network (GA^{2}LEN) analyzes the factors potentially affecting this association [16], and it has been reported that a family history of atopy may influence the development of clinical allergy, since many asymptomatic individuals do not have atopic parents [17]. This is fully confirmed in our patients: a highly significant difference (P<.0001) was found in the number of symptomatic participants with a family history of atopy (75/111 compared with 28/81). Although this finding does not explain the phenomenon, it does point us toward possible future research lines.

Monosensitization has been considered related to being asymptomatic, because of lower total and allergen-specific IgE levels and reduced type 2 helper T cell (T_H) cytokine production [18]; however, we did not find any significant differences in polysensitization between symptomatic and asymptomatic patients according to the SPT result. Of note, no asymptomatic subject was polysensitized according to the nasal IgE test result.

The lack of clinical symptoms of allergy may involve a number of factors: the quantitative or qualitative differences in allergen-specific IgE, the latter regarding functional activity and the differential expression of IgE isoforms [19]; fine specificity of the IgE response [20]; regulation of the IgE response by the T_H2/T_H1 balance and by T-regulatory cells [21]; and enhanced expression in asymptomatic individuals of FcεRI on the $CD14^{high}CD16^{dim}$ monocyte subset compared to symptomatic individuals [22].

In any case, a positive skin test result indicates that the IgE on the surface of cutaneous mast cells is reactive, because contact with an allergen elicits the release of mediators and the development of the wheal and flare reaction.

We used a different approach, consisting of the detection of specific IgE in the nasal mucosa. The results show a striking difference between symptomatic individuals, who have nasal IgE in 77% of cases, and asymptomatic individuals, who have nasal IgE in 13% of cases. The statistical analysis revealed a significant association between nasal IgE and clinical symptoms for all the allergens tested and a significant association between the results of the 2 tests for house dust mite, grass pollen, and olive pollen. No such association was observed for *Alternaria*, because of the surprisingly high number of individuals who had positive results only with the nasal IgE test, or for *Parietaria*, for which the number of positive subjects was small.

We cannot explain the absence of symptoms in 13% of asymptomatic participants despite the presence of IgE. The same is true of the 23% of symptomatic patients who experienced symptoms despite the absence of IgE in the nasal mucosa. Interestingly, the correlation between the tests for symptomatic individuals was only slight. This focuses attention on the factors underlying the kinetics of IgE, from synthesis to binding to mast cells in the skin and nasal mucosa. Further investigation of these areas is warranted.

In conclusion, we found that the absence of specific IgE in the nasal mucosa could account for the absence of rhinitis symptoms in most individuals sensitized to aeroallergens. We believe that future studies on the measurement of nasal IgE in this population should include a larger number of patients and allergens and a more detailed analysis of the possible correlation between the detection of IgE in the nasal mucosa and the development of clinical symptoms.

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Manuscript received November 24, 2008; accepted for publication September 25, 2009.

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