

Association Between Asthma and Sensitization to Allergens of *Dermatophagoides pteronyssinus*

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■ Abstract

Background: Little is known about the role of molecular diagnosis in house dust mite (HDM) allergy.

Objective: In this study, we investigated the association between the sensitization profile of adolescent and adult HDM-allergic patients and asthma in a region with high rates of exposure to HDM.

Methods: We conducted a cross-sectional study of 384 HDM-allergic patients (38.5%, males; median age, 28 years). A total of 368 patients (95.8%) had rhinitis, and 175 (45.6%) had asthma. Specific IgE (sIgE) to *Dermatophagoides pteronyssinus*, nDer p 1, rDer p 2, and rPen a 1 was measured in all patients. sIgE to *Lepidoglyphus destructor* was measured in patients (n=301) with a positive skin test result.

Results: Significantly higher concentrations of sIgE to Der p 1 and sIgE to Der p 2 were observed in patients with asthma than in those without asthma. The proportion of asthmatic patients was higher among individuals who reacted (≥ 0.35 kU_A/L) to both Der p 1 and Der p 2 (147/291, 50.5%) than among those who reacted to only 1 allergen (either Der p 1 or Der p 2, 18/55, 32.7%) or neither allergen (10/38, 26.3%, $P=.002$). Reactivity to both allergens was associated with asthma after adjusting for age and sex (OR, 2.87; 95%CI, 1.32-6.20). Higher concentrations of sIgE to *L. destructor* were observed in patients with asthma than in patients without asthma. Tropomyosin sIgE ≥ 0.35 kU_A/L was detected in only 6 individuals (1.6%).

Conclusions: *L. destructor* may be a relevant allergen in high-exposure areas. Dual sensitization (ie, IgE to both Der p 1 and Der p 2) may help to identify HDM-allergic patients who are at risk of asthma.

Key words: *Dermatophagoides pteronyssinus*. Der p 1. Der p 2. *Lepidoglyphus destructor*. Component-resolved diagnosis (CRD). Asthma.

■ Resumen

Antecedentes: El papel del diagnóstico molecular en la alergia a los ácaros no ha sido estudiado en profundidad.

Objetivo: Investigar el perfil molecular de sensibilización de pacientes adolescentes y adultos alérgicos a los ácaros del polvo doméstico y su relación con asma en una región en donde la exposición a los ácaros es importante.

Métodos: Estudio transversal en 384 pacientes alérgicos a los ácaros (38,5% varones; edad media, 28 años) de los que 368 (95,8%) padecían rinitis y 175 (45,6%), asma. Se determinó la IgE específica (sIgE) frente a *D. pteronyssinus*, nDer p 1, rDer p 2, y rPen a 1 en toda la muestra. Además, se midió la sIgE frente a *L. destructor* en 301 con una prueba positiva frente a este ácaro.

Resultados: Los pacientes con asma presentaron niveles significativamente más altos de sIgE frente a Der p 1 y a Der p 2 que aquellos que no padecían asma. La prevalencia de asma fue mayor en los pacientes con sIgE positiva ($\geq 0,35$ kU_A/L) frente a ambos Der p 1 y Der p 2 (147/291, 50,5%) que entre los sujetos que tan solo presentaron sIgE frente a uno de estos alérgenos (Der p 1 o Der p 2, 18/55, 32,7%) o ninguno de ellos (10/38, 26,3%, $p=0,002$). La detección de sIgE frente a ambos alérgenos se asoció con asma aún después de ajustar por edad o sexo (OR 2,87, 95% CI 1,32-6,20). Los pacientes con asma presentaron, asimismo, títulos más altos de IgE total y sIgE frente a *L. destructor*-sIgE. Solo 6 pacientes (1,6%) presentaron niveles de sIgE frente a la tropomiosina superiores a 0,35 kU_A/L.

Conclusiones: *L. destructor* puede ser un alérgeno relevante en áreas en las que se encuentre presente. La doble sensibilización a Der p 1 y Der p 2 podría ser de utilidad para identificar sujetos con riesgo de asma.

Palabras clave: *Dermatophagoides pteronyssinus*. Der p 1. Der p 2. *Lepidoglyphus destructor*. Asma. Diagnóstico molecular.

Introduction

The role of molecular diagnosis in house dust mite (HDM) allergy has received little attention in the literature. Today, however, the availability of natural and recombinant allergens of *Dermatophagoides* species makes it possible to investigate whether a specific molecular reactivity profile is associated with clinical manifestations in HDM-allergic individuals. Two recently published studies [1,2] suggest that ISAC microarray-based determination of IgE against various *Dermatophagoides* components may be of value in defining the risk of developing asthma in children. In the first study, the authors followed 235 children with so-called complete mite sensitization—recognition of specific IgE (sIgE) against both Der p 1 and Der p 2 allergens—from age 5 to 11 years and found a higher risk of asthma, more frequent airway inflammation, and more severe exacerbations [1]. The second study was a cross-sectional study, in which the authors found that the risk of asthma was twice as high in children with sIgE to Der p 2. The sIgE reactivity profile of older patients attracted less interest. In contrast, the authors focused more on the allegedly high degree of cross-reactivity between HDM and crustaceans through tropomyosin, although subsequent studies have shown a low degree of cross-reactivity [3]. The aim of the present study was to investigate the association between asthma and the sensitization profile of adolescent and adult HDM-allergic patients in a region with high rates of exposure to HDM.

Patients and Methods

Study Population

We conducted a cross-sectional study covering 384 consecutive HDM-allergic patients (38.5% male; median age, 28 years [range, 14-73 years; IQR, 23-35 years]) seen in the Department of Allergy of Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain between January and December 2010. Patients had been referred for the first time to our department from either primary care centers or hospitals for evaluation of a ≥ 1 -year history of symptoms of potential respiratory allergy (rhinitis, asthma, or both). The hospital has a catchment area of approximately 500 000 inhabitants (95 000 living in the city and its immediate environs and the remainder in a rural environment). The local weather is warm and humid, and mites are the most relevant inhalant allergens [4-6]. Patients were classified as having rhinitis ($n=368$, 95.8%) and asthma ($n=175$, 45.6%). Allergic rhinitis was diagnosed based on the recommendations of the ARIA 2008 update [4]. Thus, an association had to be demonstrated between a typical history of allergic symptoms (ie, rhinorrhea, sneezing, nasal pruritus, and bilateral obstruction with or without bilateral eye symptoms [itching, conjunctival hyperemia, and tearing]) and sensitization to IgE. Asthma was diagnosed based on the GEMA 2009 guidelines [5]; in addition, an increase in FEV₁ greater than 12% and 200 mL after 4 successive 100- μ g puffs of a salbutamol inhaler with a spacer was required before patients with typical symptoms could be classified as asthmatic. A methacholine bronchial challenge test was needed to confirm bronchial hyperreactivity

in 3 cases. Four patients had conjunctivitis only. Allergy to HDM was diagnosed by means of skin prick tests (SPTs) and positive serum sIgE results (≥ 0.35 kU_A/L) for *D pteronyssinus* in patients with respiratory symptoms related to indoor dust exposure. Only patients sensitized to HDM and with symptoms of HDM were included. Patients with positive SPT results for *Dermatophagoides* also underwent SPTs for *L destructor*, which is highly prevalent in the region [6-8].

Main Determinations

Total IgE was measured using latex-enhanced nephelometry in a BN-II System analyzer (Siemens). Allergen sIgE was measured using the ImmunoCAP-250 system (Thermo Fisher Scientific) and included sIgE against *Dermatophagoides pteronyssinus*, nDer p 1, rDer p 2, and rPen a 1. *L destructor* sIgE was measured in patients with a positive SPT result. Following the manufacturer's instructions, sIgE levels ≥ 0.1 kU_A/L were deemed positive, although for most analyses the classic 0.35 kU_A/L threshold level was used.

Statistical Analysis

We used the chi-square test to compare proportions, the Mann-Whitney test to compare numerical variables between groups, and the Spearman rank test to assess correlations. Receiver operating characteristic (ROC) curves were constructed to compare the diagnostic performance of allergens. Logistic regression was used for multivariate analyses.

Ethics

The study was approved by the Institutional Review Board of Complejo Hospitalario Universitario de Santiago de Compostela and complied with the recommendations of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Results

Prevalence of Sensitization and Levels of sIgE to the Components of *Dermatophagoides pteronyssinus* According to Clinical Diagnosis

While the percentage of patients reacting to Der p 1 was higher than that of those reacting to Der p 2 when the sIgE cutoff level was set at 0.1 kU_A/L (95.6% vs 85.7%), it was similar when the cutoff was set at 0.35 kU_A/L (82.6% vs 83.3% Der p 1 and Der p 2, respectively). Concentrations of sIgE to Der p 2 tended to be higher than those of sIgE to Der p 1 (median, 9.49 kU_A/L [1.65-29.1 kU_A/L] vs median 6.68 kU_A/L [0.59-24.4 kU_A/L]). A significant correlation was found between sIgE to Der p 1 and sIgE to Der p 2 ($\rho=0.812$, $P<.001$), and between sIgE to Der p 1 and sIgE to Der p 2 and sIgE to *D pteronyssinus* ($\rho=0.888$ and 0.862 , respectively, $P<.001$ in both cases). Concentrations of sIgE to Der p 1 and sIgE to Der p 2 were not significantly different between patients with and without rhinitis (data not shown). In contrast, patients with asthma displayed significantly higher concentrations of sIgE

to Der p 1 and sIgE to Der p 2 than did those without asthma (Table 1). Total serum IgE and sIgE to *D pteronyssinus* were also higher in patients with asthma (Table 1). The association between sIgE to Der p 1 and sIgE to Der p 2 and asthma was still present when the ratio of each allergen to either sIgE to *D pteronyssinus* or total IgE (Table 1) was considered in the analysis. Determination of sIgE to Der p 1 and sIgE to Der p 2 performed equally well for the diagnosis of asthma when the allergens were analyzed individually. However, when the results were positive for both allergens, the risk of asthma was higher; hence, the proportion of asthmatic patients was higher among individuals who reacted (≥ 0.35 kU_A/L) to both Der p 1 and Der p 2 (147/291, 50.5%) than among those who reacted

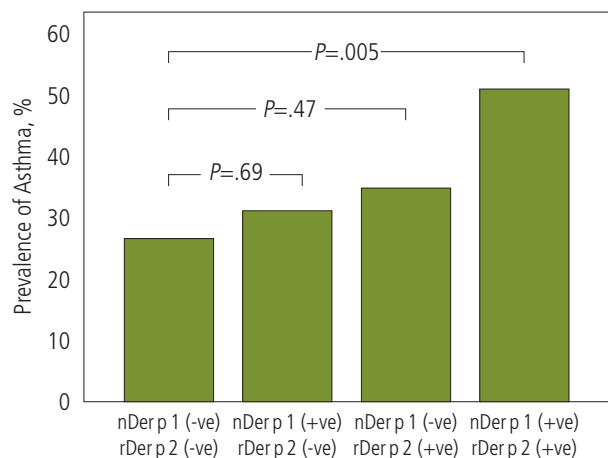


Figure. Prevalence of asthma in house dust mite-allergic individuals in relation to positivity (≥ 0.35 kU_A/L) or negativity of specific IgE to Der p 1 and Der p 2. (+ve), positive; (-ve), negative.

to only 1 allergen (Der p 1 or Der p 2, 18/55, 32.7%) or neither allergen (10/38, 26.3%, $P=.002$, Figure 1). Logistic regression analysis revealed that, whereas reactivity (≥ 0.35 kU_A/L) to only 1 allergen did not increase the risk of asthma with respect to reactivity to neither allergen (reference category; OR, 1.34 [95%CI, 0.53-3.37]; $P=.52$), reactivity to both allergens significantly increased the risk of asthma after adjusting for age and sex (OR, 2.87; 95%CI, 1.32-6.20).

Almost 81% of patients (310/384) were nonsmokers, but the proportion of smokers was slightly higher among patients with asthma than in those with rhinitis only (23.4% vs 15.8%, $P=.059$). Nevertheless, levels of sIgE to both Der p 1 and Der p 2 were similar among smokers and nonsmokers (median of 6.66 kU_A/L [0.56-34.8 kU_A/L] vs 6.72 kU_A/L [0.56-34.8 kU_A/L; $P=.811$] for Der p 1 and median of 9.47 kU_A/L [2.11-32.6 kU_A/L] vs 9.49 kU_A/L [1.51-27.1 kU_A/L; $P=.231$] for Der p 2).

Prevalence of Sensitization and Levels of sIgE to *Lepidoglyphus destructor* and Association With the Components of *Dermatophagoides* Species

sIgE to *L destructor* was determined in 301 patients and proved to be positive in (≥ 0.35 kU_A/L) in 269 patients (89.4%). The median value was 5.31 kU_A/L (0.945-15.6 kU_A/L). While the correlation between sIgE to *L destructor* and sIgE to Der p 1 was low but statistically significant ($\rho=0.249$; $P<.001$), the correlation between sIgE to *L destructor* and sIgE to Der p 2 was somewhat higher ($\rho=0.400$; $P<.001$). In addition, patients with asthma displayed higher concentrations of sIgE to *L destructor* than did those without asthma (Table 1). Serum concentrations of sIgE to *L destructor* were higher among patients living in a rural environment than among those living in an urban environment (Table 2). Conversely, concentrations of sIgE to Der p 1 were higher in patients living in an urban environment (Table 2).

Table 1. sIgE to Mites and Their Allergens and Total Serum IgE in House Dust Mite-Allergic Patients With and Without Bronchial Asthma^{a,b}

	Bronchial Asthma				P Value
	Yes		No		
	No.	Result	No.	Result	
sIgE to <i>D pteronyssinus</i> , kU _A /L	175	40.2 (11.4-85.8)	209	11.7 (3.90-29.2)	<.001
sIgE to nDer p 1, kU _A /L	175	13.2 (1.96-37.9)	209	4.06 (0.38-14.3)	<.001
sIgE to rDer p 2, kU _A /L	175	19.6 (5.41-43.9)	209	5.76 (0.51-13.7)	<.001
Ratio of sIgE to nDer p 1 to sIgE to <i>D pteronyssinus</i>	175	0.41 (0.23-0.63)	209	0.32 (0.09-0.56)	.014
Ratio of sIgE rDer p 2 to sIgE to <i>D pteronyssinus</i>	175	0.54 (0.34-0.78)	209	0.42 (0.20-0.68)	.007
sIgE to <i>L destructor</i> , kU _A /L	147	6.74 (1.64-22.0)	154	2.65 (0.63-11.9)	<.001
Total serum IgE, IU/mL	175	282.0 (117.0-655.0)	209	141.0 (70.7-258.0)	<.001
Ratio of sIgE to nDer p 1 to total IgE	175	0.055 (0.013-0.091)	209	0.035 (0.002-0.090)	.039
Ratio of sIgE to rDer p 2 to total IgE	175	0.056 (0.035-0.109)	209	0.046 (0.007-0.098)	.015

Abbreviation: sIgE, specific IgE.

^aFigures are shown as median (IQR).

^bCases with sIgE above the analytical limit (100 kU_A/L) were deemed to have 100 kU_A/L.

Table 2. sIgE to House Dust Mite and Its Allergens and Total Serum IgE in House Dust Mite–Allergic Patients Stratified According to Residence (Urban vs Rural)^{a,b}

	Residence				P Value
	Urban		Rural		
	No.	Result	No.	Result	
sIgE to <i>D pteronyssinus</i> , kU _A /L	119	25.5 (6.34-55.2)	265	18.3 (4.68-53.3)	.140
sIgE to nDer p 1, kU _A /L	119	9.39 (1.56-29.9)	265	6.36 (0.46-22.9)	.037
rDer p 2 sIgE, kU _A /L	119	9.49 (2.51-29.3)	265	9.50 (1.31-28.3)	.428
sIgE to <i>L destructor</i> , kU _A /L	89	2.31 (0.61-11.1)	212	6.18 (1.06-17.4)	.027
Total serum IgE, IU/mL	119	167.0 (83.9-477.5)	265	179.0 (86.9-428.0)	.929

Abbreviation: sIgE, specific IgE.

^aFigures are shown as median (IQR). Patients living in the city of Santiago de Compostela (95000 inhabitants) were classified as living in an urban environment, and the remainder were classified as living in a rural environment.

^bCases with sIgE above the analytical limit (100 kU_A/L) were deemed to have 100 kU_A/L.

Prevalence of Sensitization and Levels of sIgE to Tropomyosin

sIgE to tropomyosin (Pen a 1) was determined in all 384 patients and was found to be ≥ 0.10 kU_A/L in only 15 individuals (3.9%) and ≥ 0.35 kU_A/L in 6 individuals (1.6%).

Discussion

The results of this study support the hypothesis that a more severe allergic respiratory disease is associated with higher levels of both total IgE [9,10] and specific sIgE [11] in sensitized individuals. Most of the patients studied had moderate to severe allergic rhinitis (ARIA 2008 update), since no patients with mild allergic rhinitis were referred from primary care to our Allergy Department. Our results suggest that dual sensitization—the presence of sIgE to both Der p 1 and Der p 2—is associated with asthma among HDM-allergic patients. This observation is consistent with recent data from a longitudinal study indicating a higher risk of asthma in children with this pattern of sensitization [1]. It is also consistent with the findings of a recent case-control study, which showed that the more HDM allergens children recognize, the higher their risk of asthma [2]. Therefore, even though our results are more consistent with those reported by Custovic et al [1], the design of our study is more consistent with that of Resch et al [2], where the risk of asthma was found to be >2-fold higher in patients with sIgE to rDer p 2. Nevertheless, the highest risk was found among patients with sIgE to rDer p 5, which was not measured in the present study because it is not available for ImmunoCAP [2]. In addition, Resch et al [2] did not evaluate the possible association with dual sensitization. Of note, we confirmed that dual sensitization was associated with asthma in older age groups (adolescents and adults), although we have no data on the possible association between this sensitization profile and the severity of asthma. We measured sIgE to both Der p 1 and Der p 2 using the conventional ImmunoCAP test instead of the ISAC test, which was the platform used by Custovic

et al and Resch et al. Although ISAC can detect sIgE to a wide array of allergens, it is a semiquantitative analysis that is less accurate than ImmunoCAP for confirmation of HDM allergy [12]. With both platforms, Der p 1 is natural, whereas Der p 2 is recombinant, thus raising the issue of the ability of each type of allergen to recognize sIgE. Nonetheless, various studies have proven the utility of recombinant allergens from HDM in recognition of HDM-sensitized patients [13,14]. Moreover, the importance of dual sensitization was confirmed in an area of high HDM exposure and relevance in respiratory allergy (ie, Galicia in northeastern Spain) [6-8]. Consequently, the correlation between sIgE to Der p 1 and sIgE to Der p 2 was stronger than that observed in more general populations in Spain [15] [6-8]. It therefore seems reasonable to assume that different conclusions could be reached in other regions. In Germany and Austria, Der p 2 was shown to play a key role in the risk of asthma in children [2], whereas a recent study in China confirmed a relevant role for Der p 1 in the risk of asthma in both children and adults [16]. According to our data, the diagnostic performance of sIgE to Der p 1 is similar to that of sIgE to Der p 2 in HDM-allergic adolescent and adult patients. Moreover, the stronger association with asthma was observed for simultaneous sensitization to both allergens rather than for isolated sensitization to either of them. From a mechanistic standpoint, the results of the present cross-sectional study in older individuals support the hypothesis that clinical phenotypes (allergic asthma, in this case) can be predicted by the molecular nature of IgE responses to individual allergen components earlier in life [2]. From a clinical standpoint, these results may be of importance, because dual sensitization could help to identify persons at risk of asthma among HDM-allergic patients in regions with similar levels of exposure to HDM. While the same could be said of *Dermatophagoides farinae* in areas where this species is more relevant, we focused our attention on *D pteronyssinus* because it is more representative of our area [8]. Higher concentrations of sIgE to Der p 1 were observed in patients living in an urban environment, and higher concentrations of sIgE to *L destructor* in patients living in rural areas where this storage mite has been identified were

more closely associated with livestock and storage facilities than with humidity [6]. From a diagnostic point of view, and even though a low degree of cross-reactivity has been reported between *L destructor* and *D pteronyssinus*, the availability of Lep d 2 would help to clarify the relevance of this mite in clinical terms. Further studies are needed to investigate whether sensitization to specific HDM allergens could affect the composition of immunotherapy in HDM-allergic patients.

Finally, the low frequency of sensitization to shrimp tropomyosin in our sample reflects observations in our daily clinical practice and findings from other authors from the same region [17], Germany [18], and China [16]. Our previous experience with sIgE to rDer p 10 in HDM-allergic patients (unpublished results) led us to choose shrimp tropomyosin as the source for identification of sensitization to tropomyosin in the study population. Nevertheless, the prevalence found was low. Therefore, although some mite allergens are shared by crustaceans, they seem to be of less importance in the present study than in others [19,20]. The fact that the study was performed in a region with both frequent exposure to HDM and high consumption of crustaceans may have influenced the results.

In conclusion, dual sensitization to Derp 1 and Derp 2 may help to identify persons at risk of asthma among HDM-allergic patients. *L destructor* is a relevant allergen in areas with high exposure, such as the area where the study was performed.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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