

Aeroallergen Sensitization in Asthmatic Children Followed in a General Pediatric Clinic

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Abstract

Introduction: Allergic asthma is one of the phenotypes of the most common chronic disease in pediatric age. Allergic sensitization varies geographically, and its determination is important for therapeutic guidance. This study aimed to define the aeroallergen sensitization profile in asthmatic children followed in a general pediatric clinic and assess the relation between inhalant Phadiatop® with personal / family history of atopy and total serum immunoglobulin E.

Methods: This retrospective study was conducted on children with asthma aged two or older who were followed in a pediatric clinic. Personal / family history of atopy, total immunoglobulin E, Phadiatop® test results, and value of specific immunoglobulin E were analyzed in those who underwent allergic screening. The statistical analysis of data was carried out using IBM SPSS Statistics software (version 26).

Results: A total of 401 children underwent allergic screening with positive results for total immunoglobulin E (62.09%) and Phadiatop® (57.36%). The association between those was statistically significant. In children with positive Phadiatop test, the most frequent aeroallergens were *Dermatophagoides pteronyssinus* (81.30%) and *Dermatophagoides farinae* (76.52%), followed by *Dactylis glomerata* (32.61%) and *Secale cereale* (28.26%). It was found that 95.65% of children had sensitization to more than one aeroallergen. Moreover, allergic rhinitis and atopic eczema were present in 62.59% and 41.15%, respectively, and the relation between these and Phadiatop® test results was statistically significant. However, the association with family history was not established.

Discussion: We found high sensitization to domestic dust mites, particularly *D. pteronyssinus*. Aeroallergen sensitization is more influenced by allergic rhinitis than by atopic eczema and was not influenced by a family history of atopy. The association between positive results of total IgE and Phadiatop® tests was moderately significant.

Keywords: Adolescent; Child; Allergens/immunology; Antigens, Dermatophagoides/immunology; Antigens, Plant/immunology; Asthma/epidemiology; Dander/immunology; Hypersensitivity/diagnosis; Immunoglobulin E/blood; Portugal; Predictive Value of Tests

Keypoints

What is known:

- Household dust mites are the most common inhalant allergen in children with asthma in all age groups.
- Total serum immunoglobulin E levels are usually higher in allergic versus nonallergic asthma.

What is added:

- Aeroallergens sensitization is more influenced by allergic rhinitis than atopic eczema and is not influenced by a family history of atopy.
- A positive total IgE result has a moderate association with a positive Phadiatop® result.

Introduction

Asthma is the most common chronic disease of the lower respiratory tract in pediatric age, with chronic airway

inflammation being the central pathophysiological mechanism.¹ As a heterogeneous disease, asthma is usually classified into different phenotypes.² In childhood, especially in developed countries, asthma can

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have a strong association with allergies.¹ To confirm the diagnosis of allergic asthma, demonstration of allergic sensitization and the temporal relationship between allergen exposure and symptoms is mandatory.³

Although there are differences in the geographical distribution of the prevalence of sensitization to allergens, studies have pinpointed house dust mites as the most common allergens in Portugal, followed by pollens, animal epithelium, and fungi.⁴ Sensitization to allergens will be influenced by geoclimatic conditions, vegetation, and rural or urban location.⁵ Proper knowledge of individual allergic sensitization is essential, as exposure to these allergens increases the risk of exacerbations of asthma and can be an important factor in therapeutic selection, namely in the use of specific immunotherapy. Additionally, it is known that allergic sensitization has prognostic value, as it is the best marker of the persistence of the disease.⁶ Avoidance of allergens inside the home (indoor) is not always possible and is usually ineffective in the treatment of asthma. However, some strategies may have some clinical benefits, such as the removal of humidity and mold from homes and waterproof mattress protectors, to protect against fungi and mites, respectively.^{6,7}

This study aimed primarily to define the aeroallergen sensitization profile in children with asthma followed in a general pediatric clinic of a highly differentiated university hospital, the Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra. As the secondary goals, we intended to evaluate the relationship between the result of the inhalant Phadiatop® (Thermo Fisher Scientific Inc.) test with the personal and family history of atopy and the result of total immunoglobulin E (IgE).

Methods

This retrospective study was carried out in 2018, based on data recorded in the electronic clinical records (SClínico®) of children and adolescents aged 2 years or older (maximum 18 years), with a diagnosis of asthma followed in the Ambulatory Pediatrics Service - general pediatric outpatient clinic. The criteria set for the clinical diagnosis of asthma in the present study were three or more episodes of expiratory dyspnea, wheezing or cough variant asthma, with a positive response to inhaled bronchodilators.⁸ Children with other respiratory conditions or those whose asthma was followed up in another clinic were excluded from the sample.

The variables analyzed in all children with asthma who were under observation in a general pediatric clinic included gender, age at the date of consultation, and

whether or not allergic screening, including total IgE and inhalant Phadiatop®, were performed with the analysis of the specific IgE in case of positivity.

In the group of children and adolescents who underwent allergic screening, the considered variables included gender, age at screening, and personal and family history of atopy (that is, present or past personal history of allergic rhinitis or atopic eczema and history in first-degree relatives of rhinitis, atopic eczema, and/or asthma). We considered four age groups: 2-5, 6-9, 10-13, and 14-17 years.

Laboratory variables: total IgE - positive or negative, Phadiatop® - positive or negative, and sensitization profile to specific IgE.

The quantitative determination of serum total IgE was performed using immunonephelometry and determination of Phadiatop® positivity, as well as subsequent determination of aeroallergen specific IgE antibodies concentration by the fluoroenzyme immunoassay. The qualitative result of Phadiatop® was based on the cut-off value of 0.35 KU/L.⁹ The sensitization profile was described based on the results of the specific IgE included in Phadiatop®:

- *Dactylis glomerata* (*D. glomerata*) - cock's foot;
- *Secale cereale* (*S. cereale*) - rye;
- *Platanus acerifolia* (*P. acerifolia*) - platanus;
- *Populus deltoides* (*P. deltoides*) - eastern cottonwood;
- Cat hair / dander;
- Dog dander;
- *Blattella germanica* (*B. germanica*) - European cockroach;
- *Aspergillus fumigatus* (*A. fumigatus*);
- *Dermatophagoides pteronyssinus* (*D. pteronyssinus*);
- *Dermatophagoides farinae* (*D. farinae*).

The results of other specific IgE tests were not considered.

The data were recorded in the Excel software (Microsoft Office Professional Plus 2016®). A descriptive analysis of the qualitative variables, demographic characteristics of the sample, and sensitization profile was performed, determining relative and absolute frequencies. For age, measures of central tendency location (mean) and dispersion measures (standard deviation, SD) were calculated.

The statistical analysis was performed using the IBM SPSS software (version 26) for Microsoft Windows®. The sample does not follow a normal distribution (statistical tests of normality with p value < 0.05). So, the Kruskal-Wallis H nonparametric and the Dunn's tests were performed to assess the equality of the distributions of total IgE and Phadiatop® results in the different age groups and evaluate the differences between the groups,



respectively. Moreover, Cramér's V nonparametric test was used to assess the association between personal and family history of atopy and Phadiatop® results and the association between total IgE and Phadiatop®. A significance level of 0.05 (95%) adopted in this study indicated statistically significant differences.

Results

In 2018, 615 children who were diagnosed with asthma, in its different phenotypes, were observed at the general pediatric outpatient clinic, of whom 60.49% (n = 372) were male. Children were in the age range of 7 months to 17 years, with a mean ± SD age of 6.31 ± 4.25 years, of whom 527 were aged 2 years or more. The study was conducted on 401 children or adolescents with asthma who performed the allergic screening until 2018, of whom 61.10% were male and 54.61% were less than 6 years old, with a mean ± SD age of 6.04 ± 3.72 years. Their characteristics are summarized in Table 1. Only 19 (4.74%) adolescents were included in the 14-17

Table 1. Demographic and clinical characteristics of the sample and result of the allergic screening (n = 401)		
	n	%
Gender		
Male	245	61.10
Female	156	38.90
Age at screening		
2-5 years	219	54.61
6-9 years	103	25.69
10-13 years	60	14.96
14-17 years	19	4.74
Disease		
Asthma only	94	23.44
Asthma + allergic rhinitis	142	35.41
Asthma + atopic eczema	56	13.97
Asthma + allergic rhinitis + atopic eczema	109	27.18
Family history of atopy		
Present	208	51.87
Absent	176	43.89
Not available	17	4.24
Total immunoglobulin E		
Positive	249	62.09
Negative	149	37.16
Not available	3	0.75
Phadiatop®		
Positive	230	57.36
Negative	171	42.64

years age group. In addition to the diagnosis of asthma, 62.59% (n = 251) had an additional diagnosis of allergic rhinitis at some point in the follow-up, and 41.15% (n = 165) and 27.18% (n = 109) had atopic eczema or both, respectively. A family history of atopy was identified in 51.87%, and Phadiatop® and total IgE were positive in 57.36% and 62.09% of the cases, respectively.

Sensitization profile

In children with positive Phadiatop® (230/401, 57.36%), the specific IgE of all aeroallergens in the panel was determined in 60.87% and no splitting was performed in 12.17%. The sensitization profile and its classes are presented in Fig. 1 and Fig. 2, respectively. Sensitization to domestic dust mites *D. pteronyssinus* and *D. farinae* was found in 81.30% and 76.52% of the cases, respectively. Sensitization to domestic dust mites was exclusive in 36.52% of the cases, and the rest presented sensitization to other studied aeroallergens as well. In total, seven (3.04%) children had monosensitization to *D. pteronyssinus* and none to *D. farinae*.

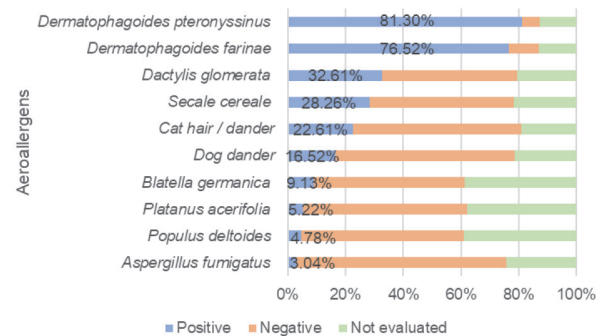
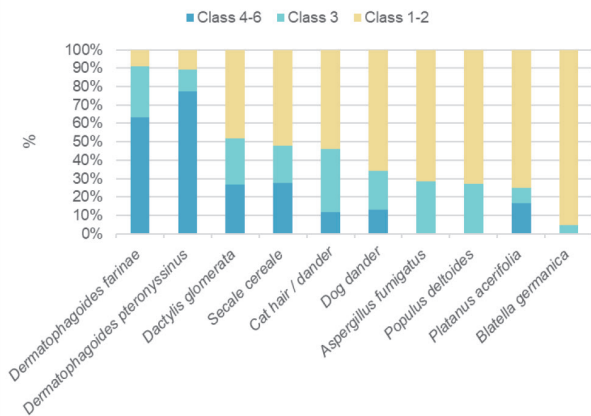


Figure 1. Sensitization profile of children with positive Phadiatop® (n = 230).



Class 4-6 - very high positive; Class 3 - high positive; Class 1-2 - low positive, moderate positive, respectively.

Figure 2. Different classes of sensitization to positive aeroallergens.

In respect of grass pollen sensitization, specific IgE was positive for *D. glomerata* (cock's foot) and *S. cereale* (rye) in 32.61% and 28.26% of the cases, respectively. Moreover, five (2.17%) cases were sensitized only to grass pollens (*D. glomerata* and *S. cereale*). The remaining aeroallergens were either negative or not evaluated. Only one (0.43%) child showed monosensitivity to *D. glomerata*, and none of the children was monosensitive to *S. cereale*.

Regarding the animal epithelia and proteins, IgE was positive for cat hair / dander and dog dander in 22.61% and 16.52%, respectively. In three cases, sensitization was demonstrated only to cat hair / dander and dog dander. One child had monosensitization to dog dander and another to cat dander / hair.

The less frequent sensitizations were observed against *B. germanica*, tree pollen *P. acerifolia* (platanus), *P. deltoides* (eastern cottonwood), and *A. fumigatus* in 9.13%, 5.22%, 4.78%, and 3.04% of the cases, respectively. There was no evidence of monosensitization to these aeroallergens.

The majority (95.65%) of children with positive Phadiatop® had sensitization to more than one aeroallergen, with 40% of the children having sensitization to aeroallergens in the same group. There were some associations between groups of aeroallergens, including simultaneous sensitization to house dust mites and grass pollen (12.61%), grass pollens and epithelia / animal proteins (8.70%), animal epithelia / proteins (8.26%) and *B. germanica* (2.61%).

In terms of class distribution, the aeroallergens *D. pteronyssinus* and *D. farinae* had higher levels of IgE (with 77.54% and 63.07% of positive cases, respectively) corresponding to class four or higher (positive-very high) (Fig. 2). In the remaining aeroallergens, the majority had lower sensitization values, with *B. germanica* standing out with 95.24% of the cases included in class one or two. The values obtained for sensitization to *P. acerifolia*, *P. deltoides*, and *A. fumigatus* corresponded mainly to class one or two in 75.00%, 72.73%, and 71.43% of the cases, respectively.

Considering the age group, it was found that the results of total IgE and Phadiatop® did not have the same distribution in all age groups (Table 2), with a statistically

significant result (for total IgE, Kruskal-Wallis H = 20.890, $p < 0.001$; for Phadiatop®, Kruskal-Wallis H = 52.493, $p < 0.001$).

There was a trend towards less evidence of atopy at preschool age. This was demonstrated by the difference in the mean of the ordinations (Kruskal-Wallis H test) and by the Dunn's test which revealed a statistically significant difference between this age group and the others, considering the results of Phadiatop®. Regarding the total IgE results, there was a statistically significant difference between the age group 2-5 years and the age groups that included children in the age range of 6-13 years. However, this difference was not found when compared with the group of older children. Sensitization distribution by age is presented in Fig. 3.

In all age groups, there was a greater sensitization to household dust mites (*D. pteronyssinus* and *D. farinae*), which was more representative in younger children (age groups 2-5 and 6-9 years). Sensitization to *B. germanica* was more expressive in children of preschool age and sensitization to *P. acerifolia*, *P. deltoides*, and *A. fumigatus* was higher in the older age groups (10-13 and 14-17 years). There was also a considerably higher sensitization to grass pollen (*D. glomerata* and *S. cereale*) in the group of older children.

Finally, it was found that 46.63%, 43.89%, 18.70%, 16.21%, 12.97%, 9.48%, 5.24%, 2.99%, 2.74%, and 1.75% of the total sample of children who were followed in the clinic and underwent allergic screening (n = 401) were sensitized to *D. pteronyssinus*, *D. farinae*, *D. glomerata*, *S. cereale*, cat hair / dander, dog dander, *B. germanica*, *P. acerifolia*, *P. deltoides*, and *A. fumigatus*, respectively. A total of 54.86% were sensitized to more than one aeroallergen.

Relationship between the result of Phadiatop® with the personal and family history of atopy and the result of tIgE

In children with asthma, a personal history of allergic rhinitis and/or atopic eczema was associated with a positive result on Phadiatop®, which was of little statistical significance. The results of the non-parametric test of association between two nominal Cramer's V variables are presented in Table 3.

Table 2. Positivity of total immunoglobulin E and Phadiatop® in different age groups

Age group	Number (n)	Positive total IgE (%)	Positive Phadiatop® (%)
2-5 years	219	52.05	41.10
6-9 years	103	72.82	74.76
10-13 years	60	80.00	80.00
14-17 years	19	63.16	78.95

IgE - immunoglobulin E.



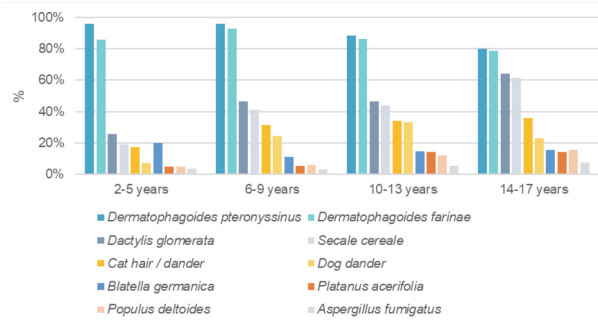


Figure 3. Profile of sensitization to aeroallergens in children with positive Phadiatop® in different age groups

region in 2018.¹⁴ Corroborating the relevance of house dust mites in the sensitization profile, we found that classes of sensitization of these allergens were higher since they were more often responsible for sensitization in isolation.

D. glomerata (cock's foot) and *S. cereale* (rye) demonstrated the most frequent outdoor aeroallergens in their study. The relevance of sensitization to grass has also been observed in other studies.¹⁴

The aeroallergen that showed the lowest prevalence of sensitization in all age groups was *A. fumigatus*, and in children with positive *A. fumigatus*, IgE levels were

Table 3. Association between the Phadiatop® result and the personal history of atopy (Cramer's V non-parametric test)

Association between the Phadiatop® result and:	Cramer's V	p value	Interpretation
- Allergic rhinitis	0.313	< 0.001	Weak positive association
- Atopic eczema	0.116	0.020	Very weak positive association
- Allergic rhinitis and atopic eczema	0.232	< 0.001	Very weak positive association

Cramer's V association coefficient varies between 0 and 1, 0 being the absence of an association and 1 a perfect association.

A family history of asthma, allergic rhinitis, and/or atopic eczema was identified in first-degree relatives in 51.87% (n = 208) of the children in the sample, with no statistically significant relationship with the Phadiatop® result (Cramer's V = 0.020, p = 0.922).

In total, 62.09% (n = 249) of children in the study had a positive total IgE value, which was found to have a moderately significant positive association with a positive Phadiatop® result (Cramer's V = 0.605, p < 0.001).

Discussion

In this study, a higher prevalence of asthma was reported in males (60.49%), in agreement with other studies.^{10,11} The sensitization profile varies according to the geographic area.¹² In the present study, a high sensitization to domestic dust mites (particularly *D. pteronyssinus* with 81.30% positive results) was demonstrated, which was consistent with other studies carried out in Portugal,^{13,14} and even those conducted in other countries outside Europe.^{15,16} The greatest sensitization to *D. pteronyssinus* and *D. farinae* was found in all age groups.

The existence of high levels of dust mites in houses and mattresses, favored by climatic and house conditions, has been pointed out as the cause of this etiology, by the narrative review¹⁷ of 2015. Although the study only includes *D. pteronyssinus* and *D. farinae*, it would be important to study sensitization to *Lepidoglyphus destructor*, a common mite in Coimbra,⁵ which was even more prevalent than *D. farinae* in the northern coastal

typically in lower classes. Although these data seem to reflect a reduced significance of this aeroallergen in pediatric asthma, there have been some reports on a possible association between the severity of asthma and sensitization to this fungus in adults.¹⁸ It would be interesting to study the likelihood of this association in pediatric age.

The vast majority of children (95.65%) were sensitized to more than one aeroallergen. Regarding the high prevalence of polysensitization,¹⁹ it should be clarified that some children had sensitization to more than one aeroallergen, but from the same group.

Higher rates of negative Phadiatop® results were observed in asthmatic preschool-aged children. It is known that allergic sensitization is a dynamic process and that its pattern changes with age.²⁰ In fact, an Italian prospective study demonstrated that 59.00% of positive results in skin tests (skin prick tests) belonged to asthmatic children at the age of 3, and this rate raised to 88.00% at the age of 11.²¹

Regarding the presence of comorbidities in the current study, a coexistence of asthma and allergic rhinitis was found in 62.59% of the children. Studies indicate that 80.00% of asthmatics have rhinitis as a comorbidity,^{8,22} and these values have also been replicated in pediatric age.²³ One possible explanation for the difference between the result of the present study and those in the literature is that nasal symptoms of younger children may not be viewed the same by their parents.

In this study, 41.15% of the children had a past or current diagnosis of atopic eczema, which is in agreement

with the results of a previous narrative review,¹⁰ that mentioned its presence in 40.00% of the cases. It is known that the relationship between atopic eczema and asthma is mainly associated with its severity, and children with severe atopic eczema are more likely to develop asthma.²⁴

We found an association (although weak and very weak) between the result of Phadiatop® and the presence of allergic rhinitis (coefficient = 0.313) and atopic eczema (coefficient = 0.116) in children with asthma. This association was higher when considering only allergic rhinitis than when allergic rhinitis and atopic eczema are present (0.232). These results should be interpreted in light of findings from other studies,^{25,26} which have demonstrated that the association between allergic sensitization and different atopic diseases depends on age and the type of allergen.

In our study, no statistically significant association was found between family history of asthma, allergic rhinitis and/or atopic eczema, and sensitization to aeroallergens. This result was unexpected since the maternal and paternal history of rhinitis, eczema, or asthma have been shown to be associated with an increased risk of sensitization to aeroallergens in children.²⁷ However, it should be noted that the sample size and the retrospective nature of the current study (incomplete records) may have influenced our results. Another possible explanation is that nasal symptoms of parents may not be as valued by themselves.

A moderately significant association (0.605) was demonstrated between the results of total IgE and Phadiatop®. Based on the results from other studies, total IgE levels are usually higher in individuals with allergic asthma.^{3,28} However, some other evidence indicates the association between asthma and total IgE levels, regardless of the presence of atopy.²⁹ Currently, the determination of total IgE levels is not considered relevant for the screening or diagnosis of allergy.^{6,30} It should be noted that the absolute value of total IgE was not considered in this study, and we only considered its positivity or negativity with respect to the reference values.

Regarding the limitations of this study, one can refer to the small sample size and the fact that it is based on a specific battery of aeroallergens, implying that the sensitization profile has been limited to the aeroallergens contained in Phadiatop®, which does not exclude a possible sensitization to others. However, the most important limitation concerns the study design and the retrospective nature of the study. Since data collection in retrospective studies is not systematized, therefore, the analysis and results are susceptible to omissions and errors. It is also important to assess the relationship between exposure to sensitized aeroallergens and clinical manifestations, since a child may not have symptoms when exposed to all aeroallergens for which he / she had a positive result in the respective tests.

Author Contributions

CV, IR, GO AND RS participated in the study conception or design.

CV and IR participated in acquisition of data. CV, IR, GO AND RS participated in the analysis or interpretation of data. CV and IR participated in the drafting of the manuscript. GO AND RS participated in the critical revision of the manuscript.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013).

Provenance and peer review

Not commissioned; externally peer reviewed

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Sensibilização a Aeroalergénios em Crianças com Asma Seguidas num Hospital Pediátrico

Introdução: A asma alérgica é um dos fenótipos da doença crónica mais comuns na idade pediátrica. O perfil de sensibilização alérgica varia geograficamente, sendo a sua determinação importante para a orientação terapêutica. O objetivo principal é definir o perfil de sensibilização a aeroalergénios em crianças com asma seguidas num hospital pediátrico e avaliar a relação entre o Phadiatop® inalante e a história pessoal / familiar de atopia e a imunoglobulina E sérica total.

Métodos: Foi realizado um estudo retrospectivo que incluiu crianças com asma com 2 ou mais anos. Naqueles que realizaram rastreio alergológico, foram analisadas a história pessoal / familiar de atopia, imunoglobulina E total, Phadiatop® e valor das imunoglobulinas E específicas. Foi realizada análise estatística com recurso ao *software* IBM SPSS Statistics (versão 26).

Resultados: Realizaram rastreio alergológico 401 crianças, com resultado positivo de imunoglobulina E total em 62,09% e Phadiatop® 57,36%. A relação entre ambos foi estatisticamente significativa. Em crianças com Phadiatop® positivo, os alergénios mais frequentes foram o *Dermatophagoides pteronyssinus* (81,30%)

e *Dermatophagoides farinae* (76,52%), seguidos de *Dactylis glomerata* (32,61%) e *Secale cereale* (28,26%). Apresentaram sensibilização a mais de um aeroalergénio 95,65%. Tinham associadamente rinite alérgica 62,59% e eczema atópico 41,15%, sendo a relação entre estes e o Phadiatop® estatisticamente significativa. Não se verificou relação com a história familiar de atopia.

Discussão: Verificámos uma elevada sensibilização a ácaros do pó doméstico, particularmente *Dermatophagoides pteronyssinus*. A sensibilização a aeroalergénios é mais influenciada pela presença de rinite alérgica do que pelo eczema atópico, não sendo influenciada pela história familiar. A associação entre imunoglobulina E total positiva e Phadiatop® positivo foi moderadamente significativa.

Palavras-Chave: Adolescente; Alérgenos/imunologia; Alérgenos Animais/imunologia; Antígenos de *Dermatophagoides*/imunologia; Antígenos de Plantas/imunologia; Criança; Asma/epidemiologia; Hipersensibilidade/diagnóstico; Imunoglobulina E/sangue; Portugal; Valor Preditivo dos Testes

