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RISK FACTORS

Patterns of aeroallergen sensitization predicting risk for asthma in preschool children with atopic dermatitis

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Abstract

Objective: Atopic dermatitis (AD) is a chronic inflammatory skin disorder mostly affecting young children. Although several studies aimed to identify the risk factors for asthma in AD children, many aspects still need to be clarified. The aim of this study was to investigate the possible risk factors for asthma at school age in 99 children with early-onset and IgE-mediated AD. **Methods:** All children performed clinical evaluation and total and specific IgE assay for a panel of inhalant and food allergens at two different times (t_1 and t_2) during preschool, and asthma diagnosis was assessed at one follow-up visit (t_3) at school age. **Results:** At t_3 , 39% of children had developed asthma. Of the variables compared, the sensitization to more than one class of inhalant allergens at t_2 (mean age = 30 months) was associated with asthma, with grass (OR = 3.24, $p = 0.020$) and cat sensitization (OR = 2.74, $p = 0.043$) as independent risk factors. **Conclusions:** The sensitization pattern of a child with early-onset AD, also within the first 2–3 years of life, can reflect his risk to develop asthma. Therefore, testing these children for the more common allergens during this time frame should be recommended to predict the evolution of atopic diseases.

Keywords

Atopic disease, IgE-mediated atopic dermatitis, inhalant allergens, risk factors, skin, specific IgE

History

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder mostly affecting infants and young children [1]. Over the last decades its prevalence has rapidly increased worldwide, and nowadays up to 15–30% of children and 2–10% of adults living in the western countries are affected [2,3]. Until now, three distinct immune phenotypes of AD have been characterized: non-IgE-associated, IgE-associated and autoimmune AD; and recent findings have highlighted the hypothesis that these subtypes might be considered as distinct and subsequent phases in the natural course of the same disorder [2]. Indeed, longitudinal studies have shown that the prevalence of the IgE-associated form tends to be higher in children than adults, due to the switch from non-IgE to the IgE-associated phase which usually occurs early in life [4–7]. Although population-based birth cohort studies have shown a relationship between the IgE-associated phenotype and the subsequent progression towards the development of respiratory allergy, the biological and immunological mechanisms underlying this phenomenon still need to be elucidated

[8–15]. Furthermore, even though it has been ascertained that one in three patients with AD develop asthma and two in three allergic rhinitis, it is still debated whether the various risk factors involved, such as genetic predisposition, impaired skin barrier, unbalanced immune system, IgE sensitization and the presence of comorbidities are linked by causal relationships or may occur independently as epiphenomena [2,16–20].

Early-onset AD, defined as the onset of the skin disease within the first 2 years of life, has been widely assessed as a determinant risk factor for asthma at school age. Nevertheless, more recent findings have strengthened the role of both early wheeze and the development of allergic sensitization as factors conditioning the progression into asthma [15,21,22]. However, the patterns of allergen sensitization which identify and predict an increased risk for asthma in children with early AD are still undefined [19].

The aim of this research is to evaluate the longitudinal course of inhalant and food allergen sensitization within the first years of life in a group of children with early-onset AD and its impact on the development of asthma at school age.

Methods**Subjects**

As part of a protocol study aimed at correlating AD genotype and phenotype (named “AllerGene2”), we recruited 184

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children with AD (aged 0–18 years) referred to the Pediatric Allergology and Pediatric Dermatology Units of the University of Bologna. As described elsewhere, at the time of enrolment most of the children ($n=112$, 61%) had moderate AD, while 37 of them (20%) showed a severe form of the disease and only 35 children (19%) had mild AD [7]. Clinical evaluation and allergometric tests were performed at the first observation within the first 5 years of age; others at intermittent times according to the clinical needs and at follow-up (mean age of follow-up 10 years). Family history suggestive for atopic diseases (AD, asthma, rhinoconjunctivitis, food allergy) was assessed at the time of the enrolment. The inclusion criteria and the complete clinical features of the whole study population are described elsewhere [6,7].

For the purposes of the present study, we included only a subset of the 184 children, including those who had referred to our Units before the age of 2 years and had therefore shown an early-onset of the disease [6].

All enrolled children fulfilled the following criteria:

- (i) early-onset disease (≤ 18 months);
- (ii) enrolment and first observation before the age of 18 months (t_1);
- (iii) at least one further observation within the age of 33 months (t_2);
- (iv) at least one follow-up visit at school age (t_3 ; mean age = 10 years old) and
- (v) diagnosis of IgE-associated AD, according to the definition proposed by Wüthrich et al. [23].

Clinical and allergometric assessment

The diagnosis of AD was made at the recruitment by a study physician (Pediatric Allergist or Pediatric Dermatologist) according to the criteria of Hanifin and Rajka [24]. Symptoms suggestive of additional atopic diseases (allergic asthma and/or rhinoconjunctivitis, food allergy) were investigated and recorded at the enrolment and at each observation. The detailed description of the clinical and allergometric evaluations of the whole study population is presented elsewhere [6,7].

Although all patients were skin-prick tested (SPT) for a panel of food and inhalant allergens [7], for the present analysis we collected exclusively data on the total and specific (s)IgE for the most common classes of inhalant and food allergens performed at t_1 and t_2 : grass pollens, house dust mite (*Dermatophagoides pteronyssinus*; *D. farinae*), cat dander, cow's milk and egg white. Total IgE levels were determined with enzyme-linked immunosorbent assay (ELISA), while sIgE levels were determined by means of ImmunoCAP1000 (Thermo Fisher Scientific, Uppsala, Sweden) in all patients' sera. Patients were considered sensitized to a specific allergen if the respective sIgE levels were >0.35 kUa/L. Asthma diagnosis was assessed at one follow-up visit (t_3) performed at school age (mean age = 10 years old) by means of clinical evaluation and was confirmed by lung function tests [25]. All patients had performed at least one spirometry evaluation with bronchodilation test (ZAN100 Rhino Flow Handy II; ZAN Ferraris, Oberthulba, Germany) during school age (mean age = 10 years old). The test was considered positive when the variation in forced expiratory volume in 1 s (FEV1)

expressed as a percentage change relative to the baseline values (Δ FEV1) before and 15 min after the inhalation of a 200 μ g of short-acting β_2 -agonists was $\geq 12\%$.

Statistical analysis

Data were stored by means of customized databases. Patients were categorized in two groups according to the development of asthma at school age. The χ^2 test and non-parametrical tests were applied when appropriate. In particular, proportions were compared by χ^2 test; mean age of onset and remission of atopic disorders and geometric mean levels of total IgE were compared by Mann–Whitney U -test. p Value <0.05 were considered significant.

Univariate and multivariate logistic regression were used to determine factors influencing the risk of asthma among the following variables: gender, parental atopy, food allergy, allergic rhinoconjunctivitis, age of onset of allergic diseases, specific allergen sensitization and total IgE levels (at t_1 and t_2) [26]. Only variables with a univariate p value <0.05 were included in the multivariate analysis. All statistical analyses were performed using the STATA[®] package (StataCorp, STATA Statistical Software: Release 7.0, Stata Corporation, College Station, TX).

Ethical approval

The research was conducted according to the principles expressed in the Declaration of Helsinki, and approved by the S. Orsola-Malpighi Hospital Ethics Committee (protocol name: AllerGene2; protocol no.: 40/2011/U/Tess). Written informed consent was obtained from all the parents or caregivers of the minors involved in the study.

Results

Characteristics of the study population at early preschool age (age ≤ 33 months)

Ninety-nine of the 184 children previously enrolled fulfilled the inclusion criteria for this study [6,7]. As stated elsewhere, the 85 patients excluded from the present analysis had all referred to our Units later (age between 2 and 5 years old) and no data are available about their first years of life; moreover, 15 of them (18%) presented a non-IgE-associated AD [6].

The first clinical and allergometric evaluation (t_1) was performed between 12 and 18 months (mean age = 15 months) and the second (t_2) between 27 and 33 months of age (mean age = 30 months). The detailed characteristics of the study population are summarized in Table 1. Most patients (67%) had at least one first-degree relative affected by atopic disease, whereas only 13% had a positive family history for AD. Most children (81%) had shown a clinical manifestation of food allergy, such as urticaria/angioedema, vomiting/diarrhoea or bronchospasm (mean age of onset = 9 months, range = 1–72 months) and the main foods involved were hen's egg (51%) followed by cow's milk (46%) and tree nuts (39%). At t_1 , 66% of patients were sensitized against at least one food (59% egg and 50% cow's milk), while 28% of children were sensitized against at least one class of inhalant allergens (18% against cat, 9% dust mites and 7% grasses). At the next observation 15 months later (t_2), we observed an almost

Table 1. Characteristics of the 99 children with early-onset IgE-associated AD enrolled in the study.

Characteristics	Total population (<i>n</i> = 99)	Asthma ^a (<i>n</i> = 39)	No asthma ^a (<i>n</i> = 60)	<i>p</i> Value ^b
Male, <i>n</i> (%)	58 (59)	22 (54)	36 (60)	0.884
Family history of atopy				
First-degree relative, <i>n</i> (%)	66 (67)	28 (72)	38 (63)	0.513
Second-degree relative, <i>n</i> (%)	22 (22)	7 (18)	15 (25)	0.564
Family history of AD, <i>n</i> (%)	13 (13)	4 (10)	9 (15)	0.705
Mean age at AD onset, months (range)	6 (1–18)	6 (1–18)	6 (1–18)	0.436
Mean age at AD remission, months (range)	61 (12–144)	74 (18–144)	49 (12–140)	0.008
Persistence of AD at school age, <i>n</i> (%)	60 (61)	22 (56)	38 (63)	0.632
Allergic rhinoconjunctivitis at school age, <i>n</i> (%)	63 (64)	30 (80)	33 (55)	0.045
Mean age at rhinoconjunctivitis onset, months (range)	58 (12–144)	58 (12–120)	58 (24–144)	0.968
Asthma at school age, <i>n</i> (%)	39 (39)	39 (100)	0	NA
Mean age at asthma onset, months (range)	66 (24–120)	66 (24–120)	0	NA
Past or present diagnosis of food allergy, <i>n</i> (%)	80 (81)	31 (79)	49 (82)	0.994
Persistence of food allergy at school age, <i>n</i> (%)	44 (44)	20 (51)	24 (40)	0.370
Mean age at food allergy onset, months (range)	9 (1–72)	13 (1–72)	6 (1–24)	0.547
Mean age at food allergy remission, months (range)	51 (12–144)	68 (36–144)	43 (12–84)	0.009
Foods avoided				
Hen's egg, <i>n</i> (%)	51 (51)	16 (41)	35 (58)	0.139
Cow's milk, <i>n</i> (%)	46 (46)	20 (51)	26 (43)	0.570
Nuts, <i>n</i> (%)	39 (39)	18 (48)	21 (35)	0.368
Fish, <i>n</i> (%)	5 (5)	2 (5)	3 (5)	0.659
Other, <i>n</i> (%)	19 (19)	9 (23)	10 (17)	0.928
Total IgE levels at <i>t</i> ₁ (UI/mL, geometric mean) ^c	103	89	110	0.605
Total IgE levels at <i>t</i> ₂ (UI/mL, geometric mean) ^c	211	234	199	0.401

^aPatients were categorized in two groups according to the development of asthma at school age.

^b*p* Value <0.05 were considered significant.

^cTotal IgE levels were determined at two different times, *t*₁ (mean age = 15 ± 3 months) and *t*₂ (mean age = 30 ± 3 months old) in all patients.

three-fold increase in the prevalence of sensitization towards airborne allergens (68% of patients were sensitized against at least one class of inhalant allergens), whereas the prevalence of food allergen sensitization showed a stable trend. As shown in Figure 1, the prevalence of grass pollen sensitization increased almost five-fold from *t*₁ to *t*₂: at *t*₂ 48% of patients were sensitized.

Characteristics of the study population at school age (mean age = 10 years old)

The mean age at the follow-up visit at school age (*t*₃) was 10 years old. Thirty-nine children (39%) had achieved a complete remission of AD, while the rest of them continue to have persistent or intermittent manifestations of the disease. Around half of patients with a previous diagnosis of food allergy had achieved tolerance, whereas 44 children (44% of the population) still followed an elimination diet. Thirty-nine patients (39%) had developed allergic asthma and 63 (64%) allergic rhinoconjunctivitis. In asthmatic children, the mean age of recovery from AD was higher (mean age = 74 versus 49 months; *p* = 0.008) and the achievement of food tolerance was delayed (mean age = 68 versus 49 months; *p* = 0.009) if compared with those without asthma.

The pattern of sensitization at *t*₁ (mean age = 15 months) showed no significant differences between asthmatic and non-asthmatic patients, while at *t*₂ (mean age = 30 months) we observed a significantly higher prevalence of sensitization against each class of inhalant allergens only in those with asthma (grass: *p* = 0.007; dust mite: *p* = 0.002; cat: *p* = 0.036). No significant differences were found in the pattern of food allergen sensitization between the two groups (Figure 2).

Analysis of risk factors for asthma at school age

We then investigated whether the development of asthma at school age was influenced by any of the following variables: gender, parental atopy, food allergy, allergic rhinoconjunctivitis, age of onset of allergic diseases, specific allergen sensitization and total IgE levels at *t*₁ and *t*₂. The complete analysis of risk factors for asthma is shown in Table 2. Of the above-mentioned variables compared, only the pattern of sensitization at *t*₂ (mean age = 30 months) was associated with asthma. Indeed, the univariate analysis showed that sensitization at *t*₂ towards two classes of inhalant allergens (grass, dust mite or cat) was significantly associated with asthma at school age (OR = 7.90, 95% CI = 1.95–32.02; *p* = 0.004) and the risk was highly increased if all the three classes were involved (OR = 28.75, 95% CI = 4.50–183.32; *p* = 0.001). Otherwise, in the multivariate logistic regression analysis only grass pollen (OR = 3.24, 95% CI = 1.20–8.78; *p* = 0.020) and cat sensitization (OR = 2.74, 95% CI = 1.03–7.27; *p* = 0.043) were independent risk factors for asthma at school age. No relation was found between asthma onset and the sensitization status towards foods.

Discussion

In this research, we investigated the natural course of inhalant and food allergen sensitization within the 5 years of life in a group of children with early-onset IgE-associated phenotype of AD and its impact on the progression into asthma. Our data showed that in this subset of high-risk children, the process of sensitization towards airborne allergens starts early in life and by the age of 30 months the status of sensitization of a child is a reliable predictor for the development of asthma at school age.

Figure 1. Prevalence over time of sensitization against the most common classes of food and inhalant allergens from t_1 (mean age = 15 ± 3 months) to t_2 (mean age = 30 ± 3 months old) in 99 children with early-onset AD.

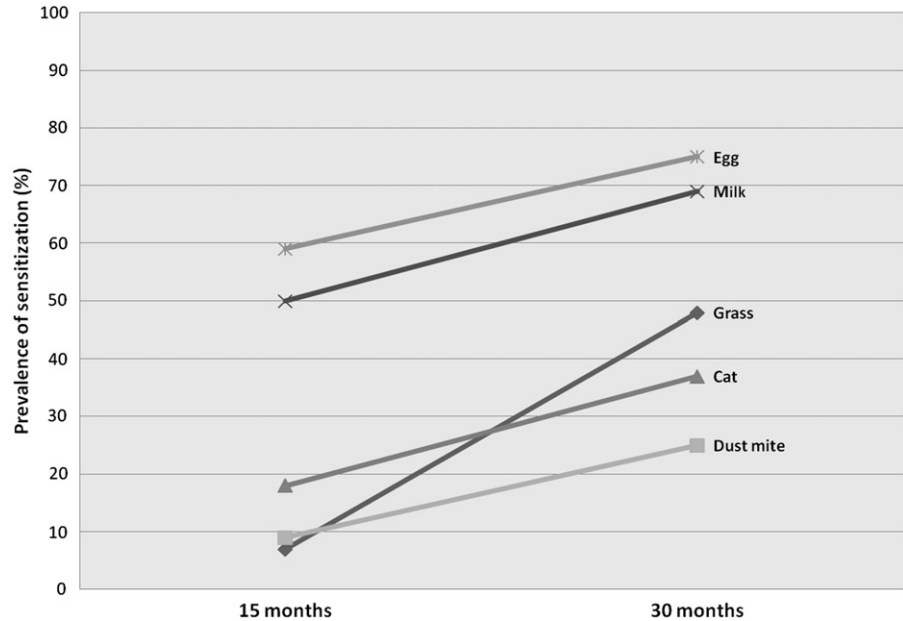


Figure 2. Differences in the patterns of sensitization to the main classes of inhalant and food allergens at two different times: (A) t_1 (mean age = 15 ± 3 months) and (B) t_2 (mean age = 30 ± 3 months old) in children with early-onset AD ($n = 99$). Patients were categorized in two groups according to the development of asthma at school age. Proportions were compared by χ^2 test. p Value <0.05 were considered significant. * $p = 0.007$; ** $p = 0.002$; § $p = 0.036$.

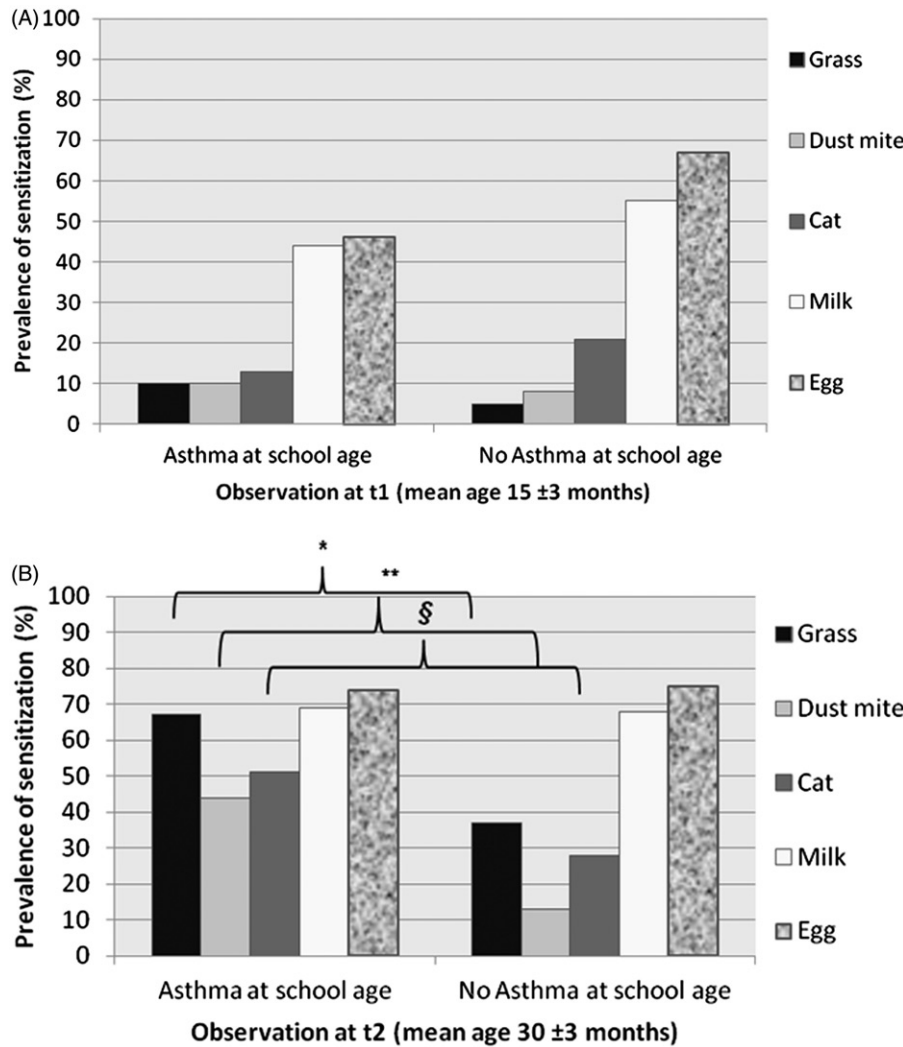


Table 2. Analysis of risk factors for asthma at school age in 99 children with early-onset AD.

	OR	95% CI	p Value ^a
Univariate analysis			
Male sex	0.82	0.36–1.87	0.650
Family history of atopy			
First-degree relative	1.38	0.51–3.70	0.521
Second-degree relative	0.32	0.09–1.04	0.059
First and/or second degree relative	0.63	0.17–2.23	0.475
Allergic rhinoconjunctivitis	0.67	0.29–1.52	0.344
Food allergy	7.75	0.95–63.25	0.056
Foods avoided			
Hen's egg	0.45	0.17–1.17	0.106
Cow's milk	1.60	0.63–4.05	0.314
Nuts	1.84	0.74–4.58	0.187
Fish	1.05	0.16–6.71	0.953
Other	1.55	0.54–4.40	0.407
Inhalant allergen sensitization at t_1^b			
Grass	3.22	0.65–15.82	0.148
Dust mite	1.76	0.42–7.25	0.434
Cat	0.71	0.22–2.28	0.567
Two inhalants	5.33	0.51–55.12	0.160
One inhalant	0.77	0.26–2.24	0.642
Food allergen sensitization at t_1^b			
Cow's milk	1.25	0.43–3.60	0.678
Hen's egg	0.75	0.23–2.38	0.625
Two foods	0.44	0.11–1.70	0.239
One food	0.24	0.05–1.15	0.075
Inhalant allergen sensitization at t_2^b			
Grass	4.25	1.72–10.48	0.002
Dust mite	5.59	2.07–15.08	0.001
Cat	3.21	1.33–7.72	0.009
Three inhalants	28.75	4.50–183.32	0.001
Two inhalants	7.90	1.95–32.02	0.004
One inhalant	2.53	0.70–9.07	0.154
Food allergen sensitization at t_2^b			
Cow's milk	1.24	0.48–3.19	0.650
Hen's egg	1.19	0.42–3.35	0.733
Two foods	0.76	0.22–2.64	0.672
One food	0.22	0.04–1.06	0.060
Multivariate analysis ^c			
Inhalant allergen sensitization at t_2^b			
Grass	3.24	1.20–8.78	0.020
Dust mite	2.91	0.97–8.73	0.057
Cat	2.74	1.03–7.27	0.043

^ap Value <0.05 were considered significant.^bSpecific IgE towards inhalant and food allergens were determined at two different times, t_1 (mean age = 15 ± 3 months) and t_2 (mean age = 30 ± 3 months old) in all patients.^cOnly variables with a univariate p value <0.05 were included in the multivariate analysis.

Within our study population, two factors seem to determine the progression to asthma: on the one hand, (i) the early development of a specific pattern of sensitization against inhalant allergens, with grass pollen and cat as independent risk factors for asthma and, on the other, (ii) the simultaneous sensitization to multiple classes of airborne allergens (at least two from among grass pollen, dust mite and cat). As novel finding, these data emphasize the role of seasonal allergens (grass pollen) in addition to perennial allergens (dust mites and cat) in the development of asthma.

Previous longitudinal and cross-sectional studies highlighted the key role of early sensitization as a determinant factor for asthma. Illi et al. [21], while investigating the natural course of AD from birth to school age in children from the German Multicenter Atopy Study (MAS) cohort, found that early-onset AD could not be considered, per se, an

independent risk factor for subsequent asthma, whereas the presence at age 2 years of wheeze and specific sensitization patterns (wheat, cat, mite, soy or birch) were significant predictors for asthma at age 7 years [15]. Supporting these findings, a further analysis of MAS patients showed that sensitization to perennial allergens (dust mite, cat and dog hair) within the first 3 years of life was associated with impairment of lung function at school age. In contrast, children with wheeze, but not atopic sensitization, tended to lose respiratory symptoms during school age and had normal lung function at puberty. More recent studies, focusing on the complexity and variability of the IgE responses to multiple allergens throughout childhood, have identified multiple atopy phenotypes, among which only those characterized by early sensitization to a broad panel of allergens proved to be a high-risk factor for asthma [27,28].

In line with our findings, a recent cross-sectional study on children and adolescents from USA with active AD, showed an increased risk for asthma in children with sIgE to cat, but no association was proven between egg and/or cow's milk sensitization and wheeze [22]. Nevertheless, the role of food allergy cannot be denied. Indeed, our data showed that children with asthma outgrow food allergy later than their non-asthmatic peers (mean age = 68 versus 49 months; $p = 0.009$). Moreover, as reported by the above-mentioned analysis of an MAS cohort, children with early-onset AD and wheeze show a peculiar sensitization pattern at age 2 years with sIgE against less prevalent allergens, including foods like wheat or soy [15]. Furthermore, a previous retrospective study performed by our group within an unselected population of children with AD enrolled during the eighties, showed that egg white sensitization by the age of 3 years was associated with both asthma and rhinoconjunctivitis at puberty [18]. This discrepancy with the present results may be explained by the fact that the aforementioned study enrolled patients with a lower rate of IgE-mediated sensitization at baseline (only 37% of children were sensitized to foods whereas 26% to airborne allergens), while in our current study we had selected exclusively a high-risk population (early-onset and IgE-mediated AD). As expected, we found a higher rate of children who developed asthma and rhinoconjunctivitis than in our previous study (39 versus 34% and 64 versus 57%, respectively). These data support the evidence that the early onset of the skin disorder in association with atopic sensitization widely promotes the progression towards asthma [11–13,19].

As stated in the “Methods” section, our analysis did not take into account the results from SPT, whereas only the results of sIgE testing were reported. In fact, although we had ascertained a good concordance between the two tests within our study population (applying a cutoff value 0.35 kUa/L for sIgE), sIgE measurement represents a more standardized laboratory assay than SPT and provides quantitative results [29]. Moreover, despite its higher sensitivity, the wide variability associated with SPTs (e.g. age, skin reactivity, presence of active eczema, operator) may have affected the results and the subsequent statistical analysis [29].

As previously mentioned, our analysis highlighted the role of grass pollen sensitization in addition to perennial allergen sensitization (dust mites and cat) as relevant risk factors for

asthma. These data, apparently in contrast with previous reports, reflect the different exposure and sensitization rates across different countries, with a subsequent impact on the sensitization profiles of the living population [30]. As reported in the Global Allergy and Asthma European Network (GA²LEN) survey, the rates of sensitization to grass pollens and to dust mites are equivalent (34%) within asthmatic patients living in Southern Europe, while in central countries a higher prevalence of dust mite allergy was reported [31]. Despite this, these data should be reconfirmed on a larger scale population, since the small sample size of the present study might have affected the results of the univariate analysis.

Conclusions

In conclusion, our findings help reinforce the concept that the process of sensitization to airborne allergens can start early in life in children with AD and, by the first 2–3 years of age, the sIgE sensitization pattern of a child is a reliable picture of the risk to evolve into asthma. Before this age, the prevalence of sIgE sensitization to inhalant allergens is still too low and not useful as a biomarker to define which subset of patients is at higher risk [32]. Therefore, children with early-onset AD should be tested for the more common and regional environmental allergens, preferably between 2 and 3 years of age since this phase of life represents the time frame during which inhalant allergen sensitization mainly appears [29,33]. Finally, it should be underlined that these findings only take into account the results of serum sIgE assay, while further investigations are needed to evaluate its reproducibility with SPT.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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