ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803-5253

REGULAR ARTICLE

Atopic dermatitis is associated with a fivefold increased risk of polysensitisation in children

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Keywords
Atopic dermatitis, Polysensitisation, Skin barrier, Specific immunoglobulin E, Transcutaneous sensitisation

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Received
29 August 2016; revised 12 December 2016; accepted 21 December 2016.

DOI:10.1111/apa.13729

ABSTRACT

Aim: It has been hypothesised that in atopic dermatitis, the dysfunctional skin barrier facilitates the transcutaneous presentation of allergens to the immune system. This study examined whether atopic dermatitis increased the likelihood of polysensitisation, namely sensitisation to five or more allergens.

Methods: We examined the electronic hospital charts of 1743 children aged 0–17 years who had visited primary or secondary care physicians with allergic symptoms, whose blood was examined for the presence of specific immunoglobulin E (IgE) to the 10 most common inhaled and food allergens and whose files contained documentation of the presence of atopic dermatitis and other skin disorders. Sensitisation was defined as a specific IgE level of ≥0.35 kU/L.

Results: Polysensitisation was more common in children with atopic dermatitis (268/1197, 22.4%) than those without (30/546, 5.5%, $p < 0.001$). This remained significant after adjustment for gender and age in a multiple logistic regression model (odds ratio: 5.63, 95% confidence interval 3.77–8.40). Other skin disorders did not show an increased risk of polysensitisation (5/97, 5.2%).

Conclusion: Polysensitisation was considerably more common in children with atopic dermatitis than those without. This supports the hypothesis that sensitisation occurs through a defective skin barrier and appears to be specific for atopic dermatitis.

INTRODUCTION

Atopic dermatitis (AD) is usually the first clinical manifestation of atopic syndrome, and children with AD are at increased risk of developing food allergies, allergic rhinitis and asthma. It has been hypothesised that the defective skin barrier in infants with AD facilitates the transcutaneous presentation of allergens to the immune system, which could then increase the likelihood of allergic sensitisation and clinical allergies (1). The skin protein filaggrin is of key importance for the proper functioning of the skin barrier, and the filaggrin gene mutations are associated with a three times higher risk of AD in children(2). In addition, filaggrin mutations are associated with a more severe and persistent form of AD and are strongly associated with atopic disease in later life (3–5). In patients with AD, filaggrin mutations increase the risk of developing a peanut allergy, asthma, allergic rhinitis and allergic sensitisation (6,7).

Early-onset AD in children increases the risk of developing allergic sensitisation (8,9), which can be identified through skin prick testing or by assessing specific immunoglobulin E (IgE) levels in blood samples. Approximately one in four sensitised children show sensitisation to five or more inhalants or food allergens, namely polysensitisation (10), and this is associated with more severe symptoms of allergic disease (10,11). AD is associated with a higher likelihood of clinical allergy in sensitised children (12,13). Although AD has been identified as a risk factor for polysensitisation in adults, to our knowledge this association has never been studied in children (14).

Abbreviations
AD, Atopic dermatitis; CI, Confidence interval; IgE, Immunoglobulin E; IQR, Interquartile range; OR, Odds ratio; SD, Standard deviation.

Key notes

- We investigated whether atopic dermatitis and other skin disorders increased the likelihood of polysensitisation, which is sensitisation to five or more allergens, in 1743 children aged 0–17 years.
- Atopic dermatitis was associated with a fivefold increased risk of polysensitisation, but other skin disorders were not.
- The skin barrier defect in atopic dermatitis appears to be specific when it comes to facilitating transcutaneous sensitisation to allergens in children.

The aim of this study was to examine the relationship between polysensitisation and AD in children of all ages. We hypothesised that AD would be associated with polysensitisation.

METHODS

Patients

This was a retrospective cross-sectional electronic patient record analysis of children aged 17 or younger who were referred by their primary or secondary care physician to our hospital's clinical laboratory for an allergy screening test or testing for specific IgE to one or more allergens between January 2004 and May 2010. In the Netherlands, specific IgE testing is the preferred method for assessing allergic sensitisation in children and skin prick testing is uncommon. The clinical laboratory in Isala was the only laboratory in the catchment area of the hospital that performed specific IgE testing during the study period. We only included patients' records if they contained information about the presence or absence of AD and other skin disorders.

Specific IgE testing

The ImmunoCap system (Thermo Fisher, Uppsala, Sweden) was used for specific IgE testing. Sensitisation was defined as a specific IgE concentration of ≥0.35 kU/L. We collected data on specific IgE testing for the ten most common food and inhaled allergens – cows' milk, hens' eggs, wheat, soy, peanut, house dust mite, grass pollen, tree pollen, dog dander and cat dander – in accordance with our earlier work (15). If more than one test was performed on a child, we only used the most recent test result.

Clinical and demographic data

We extracted the following from each electronic patient record: the presence or lifetime absence of symptoms or doctor's diagnosis of AD and other skin conditions and the patient's age and gender.

Ethical considerations

Under Dutch law, this retrospective analysis was exempt from ethical review, which was confirmed in writing by the hospital's medical ethical review board.

Statistical analysis

The statistical analysis was performed with SPSS for windows version 22.0 (SPSS Inc, Chicago, Illinois, USA). Differences between proportions were analysed using the chi-square test. Due to the skewed distributions of age and IgE levels, we used nonparametric methods for the analysis. Multiple logistic regression was used to examine the association between AD and polysensitisation and to adjust this for age and gender.

RESULTS

Over the study period, specific IgE testing for the 10 most common inhaled and food allergens was carried out on 7825 patients. Information on the lifetime presence or absence of AD and other skin disorders was found in 1743 of these patients' files (22.3%). The age of the children whose files contained information on the prevalence skin disorders was significantly lower with a mean and standard deviation (SD) of 8.5 (5.4) years than that of the patients whose files did not contain information on skin disease (9.5 years and 4.9 years, $p < 0.01$). The gender distribution was not significantly different between the two groups ($p = 0.063$). The prevalence of sensitisation to one or more allergens was higher in children whose files contained information on skin diseases (57.2%) than in those whose files did not contain such information (45.5%, $p < 0.001$).

The mean (SD) age of the 1743 children whose files were selected for further analysis was 8.5 (5.4) years. There were 876 girls (50.3%). Table 1 gives the frequency distribution of specific IgE test results.

Polysensitisation was largely explained by sensitisation to inhaled allergens. In 168 polysensitised children (56.4%), polysensitisation was fully explained by five positive inhaled allergen tests. Polysensitisation that was only caused by food allergen sensitisation was found in 56 children (18.8%). In the remaining 74 children (24.8%), polysensitisation was due to positive tests to food and inhaled allergens.

Children with AD were significantly younger, with a median age of 6.3 years and interquartile range (IQR) of 3.5–11.8 than children without AD (median age: 10.7 years, IQR 4.8–16.0, $p < 0.001$). The prevalence of polysensitisation was 17.8% in 0- to four-year-olds, 53.4% in four- to 11-year-olds and 28.9% in 12- to 17-year-olds. Polysensitisation was most commonly seen in children of four to 11 years of age ($p < 0.001$) with an odds ratio (OR) of 1.68 and 95% confidence interval (95% CI) of 1.31–2.16. The boys in our study were younger with a mean (SD) age of 7.1 (4.8) years than girls at 9.9(5.6) years ($p < 0.001$), and the boys had a higher prevalence of AD (n = 626, 52.3%) than the girls (n = 571, 47.7%, $p = 0.003$). Polysensitisation

Table 1 Prevalence of sensitisation in 1743 children with allergic symptoms

		Positive tests		
Sensitisation pattern	Number (%)	Number of positive tests	Number of children	%
No sensitisation	746 (42.8)	0		
Sensitisation to one allergen	217 (12.4)	1		
Sensitisation to 2–4 allergens	482 (27.7)			
		2	201	41.7
		3	134	27.8
		4	147	30.5
Polysensitisation (sensitisation to five or more allergens)	298 (17.1)			
		5	122	40.9
		6	44	14.8
		7	42	14.1
		8	40	13.4
		9	21	7.1
		10	29	9.7

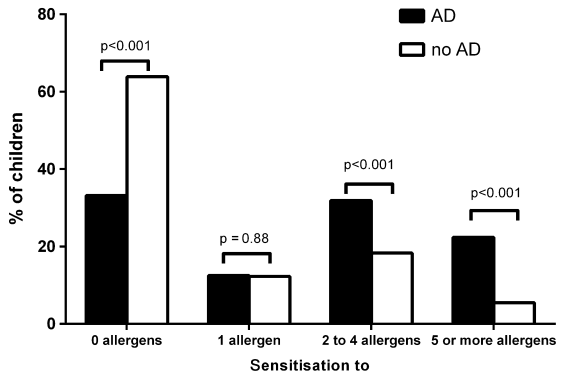

Figure 1 Prevalence of atopic dermatitis in children with sensitisation to 0, 1, 2 to 4 or 5 or more allergens. AD = atopic dermatitis.

was equally common in boys (163/869, 18.8%) and girls (135/874, 15.4%) (p = 0.075, OR: 1.26, 95% CI: 0.98–1.62).

Figure 1 shows the relation between sensitisation patterns and AD. In children with AD, polysensitisation was considerably more common (268/1197, 22.4%) than in children without AD (30/546, 5.5%) (p < 0.001, OR: 4.96, 95% CI: 3.35–7.35). This association between AD and polysensitisation remained significant after adjustment for gender and age in a multiple logistic regression model (OR: 5.63, 95% CI: 3.77–8.40). The risk of sensitisation to two or more allergens was also strongly increased in children with AD (OR: 4.44, 95% CI: 3.49–5.64, p < 0.001).

Other skin conditions were diagnosed in 97 children, most commonly (62%) other forms of dermatitis, namely orthoergic contact, seborrhoeic and nummular dermatitis. Sensitisation was found in 33 children with these other skin disorders (34.1%): nine of these (9.3%) were sensitised to one allergen, 19 (19.6%) to 2–4 allergens and five (5.2%) to five or more allergens. The prevalence of polysensitisation in children with these other skin conditions was comparable to that in children without AD (5.5%, p = 0.97), but much lower than in those with AD (p < 0.0001).

DISCUSSION

This study showed that children with AD faced a considerably higher risk of being sensitised to multiple allergens. Polysensitisation was more than five times as common in children with AD than in those without. Other skin disorders were not associated with polysensitisation so it appears this effect was specific for AD.

The prevalence of polysensitisation in the present study – 29.9% of all sensitised children – was slightly higher than in our previous study in the same root population (21.5%) (10). This is likely to have been due to selection issues, because we only included children in this study if the presence or absence of AD was recorded on their chart. Because our study sample consisted of children referred for allergy testing because of allergic symptoms, and we only included children whose physicians recorded data on the lifetime prevalence of AD on the chart, the prevalence of polysensitisation in our studies is likely to be higher than it would be in a general unselected population. Although polysensitisation is common (10), it has been the subject of few studies and its clinical relevance is poorly understood. Different definitions have been proposed, such as sensitisation to two or more (11,16) or five or more allergens (10). In our study, AD was significantly associated with the risk of sensitisation to two or more allergens, but even stronger with sensitisation to five or more allergens.

The most likely mechanism that explains why children with AD show more polysensitisation is transcutaneous sensitisation (1,17,18). In children with early-onset AD, allergen sensitisation is beginning to emerge within weeks to months of the onset of AD (19). This is thought to be due to the transcutaneous presentation of allergens through the defective skin barrier in AD. Filaggrin mutations play a major role in proper functioning of the skin barrier (3–5). Although filaggrin mutations are often seen in between 14 and 48% of European children with AD (20) and are important in transcutaneous sensitisation, not all children with AD have filaggrin mutations. The lack of association between polysensitisation and other skin disorders suggests that the skin barrier defect promoting transcutaneous sensitisation is specific for AD. The mechanisms of transcutaneous sensitisation in AD have not been fully explained, but interleukin-33 appears to play a role (21). Further research is needed in this area to help identify potential strategies for preventing such transcutaneous sensitisation.

Previous research has showed that the severity of AD was associated with the number of positive IgE tests (4,8,18,22). It can be assumed that the immune system is exposed to more allergens when there is a dysfunctional skin barrier in the early stages of life. As 45% of children with AD develop it during the first six months of life (23), and early-onset AD is associated with multiple sensitisations later in life (24), this may help to understand why children with AD show the highest prevalence of polysensitisation between the ages of four and 11 years.

The few studies that have been published about polysensitisation in children showed an association with a more severe atopic phenotype (11,25). Asthmatic children with polysensitisation experienced more complaints and a poorer response to immunotherapy than those with monosensitisation (11). The combination of multiple sensitisation and early-onset AD has been identified as an important risk factor for severe asthma in children (19). Together with the results of the present study, this suggests that transcutaneous sensitisation to multiple allergens occurs early in life in children with AD and this is associated with a more severe atopic and asthmatic phenotype later in life.

To our knowledge, this is the first study to investigate the relation between AD and polysensitisation in children. The main strengths of this study were the large sample size and the fact that the cohort consisted of children referred for allergy testing because of complaints associated with allergies, yielding a population representative of that experienced in clinical care of children with allergic symptoms, and supplementing data from general population-based studies. Because of the retrospective design of this study, we had no

standardised clinical data and no data on the severity of AD or the presence of filaggrin mutations. Only including records with documented evidence of a lifetime prevalence of AD resulted in us selecting more a commonly sensitised and slightly younger population than the root population of children for whom sensitisation test results were available. This limits the generalisability of our findings.

Practitioners should realise that children with AD have a higher likelihood of showing polysensitisation than children without AD. The presence of polysensitisation suggests the likelihood of a more severe atopic phenotype, but it complicates the clinical interpretation of individual specific IgE levels (10), particularly if the threshold of sensitisation is set as low as 35 kU/L.

CONCLUSION

This study showed a fivefold increased prevalence of polysensitisation in children with AD compared to children without AD. This supports the hypothesis that allergen sensitisation could be due to a dysfunctional skin barrier early in life, which appears to be specific for the skin barrier dysfunction in AD.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest to disclose

FUNDING

No specific funding was received for this study.

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