Associations between sensitization to perennial/seasonal allergens and childhood asthma

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Introduction

Childhood asthma is an important public health problem worldwide [1]. Risk factors include genetic, environmental, and host factors. Common risk factors are: sex, socioeconomic status, exposure to tobacco smoke [2], exposure to air pollution [3], diet [2, 4], obesity [5], allergic sensitization, family structure, and exposure to animals [2] as well as a family history of atopic diseases [2, 6]. To date, most research has focused on the association of asthma with multiple sensitizations, but the type and number of allergen sensitization are unknown [7]. Few studies have investigated home environmental exposures at school-age as putative risk factors for asthma development in adolescence [8]. However, this may be highly relevant in childhood, where a wide range of total serum or specific IgE (sIgE) levels is often detected.

We aimed to find out the sensitization to which inhalant allergens (perennial or seasonal) was associated with asthma and allergic rhinitis in children.

Materials and Methods

Study design

This was a cross-sectional, retrospective study. We evaluated data from medical documentation of 6,000 children (aged 6 – 18 years) with physician-diagnosed asthma and/or allergic rhinitis who had attended our allergy outpatient clinic between January 2005.
and December 2012. Into the analyses we included those subjects who, during diagnostic procedures, had specific IgE test done to confirm allergen sensitization. Confirmation of asthma/allergic rhinitis diagnosis was made previously by the allergists according to the standard definitions of diseases in the latest guidelines [9, 10] or their respective previous versions (due to the fact that patients had been admitted since January 2005). The retrospective analysis of the study for the evaluation of data from medical documentation of children was approved by the Medical Ethics Committee of the Medical University of Lodz. The study was registered on: www.ClinicalTrials.gov, with ClinicalTrials.gov ID: NCT01805635.

**Allergen sensitization**

Allergen sensitization was defined as specific IgE of ≥ 0.35 KU/L for at least one of the tested allergens (chemiluminescence method (CLIA), Immulite 2000, XPI, Siemens, Germany). For purpose of the study, we defined perennial allergy as presence of serum IgE of ≥ 0.35 KU/L specific for the perennial allergens dust mites, molds, cat and dog dander; seasonal allergy was defined as presence of serum IgE of ≥ 0.35 KU/L specific for the seasonal allergens grasses, wild grasses, and tree pollen.

**Statistical methods**

The associations between the diagnosis allergic rhinitis or asthma and the serum level of specific IgE were analyzed using univariate followed by multivariate logistic regression. Cut-off points with optimal discrimination (the highest sensitivity and specificity) of specific IgE levels were calculated in ROC curve analysis. All statistical analyses were performed using StatSoft Statistica for Windows, release 8.0 (StatSoft, Inc., Tulsa, USA), p < 0.05 was used as a definition of statistical significance.

**Results**

We included 5,076 children in the analysis (absolute number of patients who had specific IgE results). Clinical characteristics are given in Table 1.

In the first step we implemented logistic regression analysis to find out the sensitizing allergens most closely related to allergic rhinitis/asthma. Analyses for perennial and seasonal allergens were made independently. The results of the multivariate models are presented in Table 2. We showed that among the seasonal allergens, only sensitization to timothy or birch significantly changed the prevalence of allergic rhinitis and asthma diagnosis (Table 2). Among the perennial allergens, house dustmite or cat were most closely related to both allergic rhinitis and asthma in our population (Table 2).

In the next step we assessed the relationship between specific IgE level and the diagnosis of allergic rhinitis/asthma among atopic children. Area under the receiving operating characteristic (ROC) curve for serum levels of sensitizing allergens as discrimination threshold for allergic rhinitis and asthma diagnosis are given in Table 3 and Table 4, respectively. Results of the ROC curve analysis showed that among atopic children, specific IgE levels of seasonal and perennial allergens do not significantly change the
Table 2. Associations between allergy profile and diagnosis of allergic rhinitis/asthma. Data is presented with OR (95%CI) as a result of multivariable logistic regression analysis; only statistically significant predictors of allergic rhinitis/asthma are given (final models).

|                       | ORa    | 95% CI   | p   | ORb    | 95% CI   | p   |
|-----------------------|--------|----------|-----|--------|----------|-----|
| **Seasonal allergens**|        |          |     |        |          |     |
| Timothy               | 1.012  | 1.008 1.016 | <0.0001 | 1.011 1.007 1.014 | < 0.0001 |
| Birch                 | 1.009  | 1.004 1.013 | 0.0003 | 1.006 1.001 1.010 | 0.0176 |
| **Perennial allergens**|        |          |     |        |          |     |
| House dust mite       | 1.011  | 1.006 1.015 | <0.0001 | 1.014 1.010 1.018 | < 0.0001 |
| Cat                   | 1.014  | 1.008 1.021 | <0.0001 | 1.009 1.003 1.016 | 0.0037 |

aDependent variable – diagnosis of allergic rhinitis; bdependent variable – diagnosis of asthma.

Table 3. Area under the ROC curve for serum levels of sensitizing allergens as discrimination threshold for the diagnosis of allergic rhinitis.

| Serum level of sensitizing allergens | Areaa | 95% CI   | p-levelb | Cut-offc |
|-------------------------------------|--------|----------|-----------|----------|
| House dust mite                     | 0.59   | 0.56 0.62 | < 0.0001 | 5.20     |
| Cat                                 | 0.57   | 0.52 0.61 | 0.0031    | 12.60    |
| Birch                               | 0.58   | 0.54 0.62 | 0.0001    | 8.90     |
| Timothy                             | 0.56   | 0.53 0.60 | 0.0001    | 6.00     |

aArea under the ROC curve; bnull hypothesis: true area = 0.5; cSIgE level [IU/L] with highest area under the ROC curve.

Table 4. Area under the ROC curve for serum levels of sensitizing allergens as discrimination threshold for the diagnosis of asthma.

| Serum level of sensitizing allergens | Areaa | 95% CI   | p-levelb | Cut-offc |
|-------------------------------------|--------|----------|-----------|----------|
| House dust mite                     | 0.61   | 0.58 0.65 | < 0.0001 | 9.90     |
| Cat                                 | 0.55   | 0.50 0.59 | 0.0332    | 12.60    |
| Birch                               | 0.53   | 0.49 0.57 | 0.1347    | 4.50     |
| Timothy                             | 0.52   | 0.48 0.55 | 0.3350    | 2.50     |

aArea under the ROC curve; bnull hypothesis: true area = 0.5; cSIgE level [IU/L] with highest area under the ROC curve.

Finally we checked for the cumulative effect of multiple allergens. As was expected, sensitization to more than one allergen significantly increased the prevalence of allergic rhinitis and asthma diagnosis. However, this phenomenon was visible only for perennial allergens (Table 5).

Table 4. Area under the ROC curve for serum levels of sensitizing allergens as discrimination threshold for the diagnosis of asthma.

| Serum level of sensitizing allergens | Areaa | 95% CI | p-levelb | Cut-offc |
|-------------------------------------|--------|--------|-----------|----------|
| House dust mite                      | 0.61   | 0.58 0.65 | < 0.0001 | 9.90     |
| Cat                                  | 0.55   | 0.50 0.59 | 0.0332    | 12.60    |
| Birch                                | 0.53   | 0.49 0.57 | 0.1347    | 4.50     |
| Timothy                              | 0.52   | 0.48 0.55 | 0.3350    | 2.50     |

aArea under the ROC curve; bnull hypothesis: true area = 0.5; cSIgE level [IU/L] with highest area under the ROC curve.

Discussion

To date, only few studies have considered polysensitization as a risk factor for asthma development in prediction models and those were performed in populations from affluent countries. We aimed to find out the sensitization to which inhalant allergens (perennial or seasonal) was associated with asthma and allergic rhinitis in a population of Polish children. Our findings showed that only Dermapthagoides farinae, cat dander, birch, and Timothy grass allergens were associated with a diagnosis of asthma and allergic rhinitis. We determined the cut-off levels of specific seasonal and perennial IgE with optimal diagnostic accuracy.

Our results cannot be compared to other studies due to the lack of studies with similar methodology. Kihlström et al. [11] found that exposure to birch pollen in early infancy may increase the risk of atopic diseases in childhood. Other authors state that persistent pollen exposure in early life appears to increase the risk of asthma and hay fever in children [7, 12, 13, 14]. This difference to our study may be due to the fact that these assessments were made in completely different populations and that we have not examined the effect of family history by season of birth.

Our results suggest that among perennial allergens, house dust mite and cat were most closely related with both allergic rhinitis and asthma in our population. Our results are similar to Maheswaran et al.’s [15], who confirmed that early exposure to dust mite allergens is a risk factor for atopic asthma and bronchial hyperresponsiveness in adolescents. In two large population-based cohort studies from Germany and South England
no significant association was found between early pet exposure and asthma at the age of 5 – 7 years. There are several studies discussing the idea that early exposure to furry pets may protect children from later allergy [18, 19, 20].

We found that among atopic children, the level of specific IgE to seasonal allergens does not significantly change the prevalence of the diagnosis of childhood asthma. Contradictory, Chiu et al. [21] report a significantly increased risk for the development of asthma and rhinitis in children with sensitization to inhalant allergens after the age of 2 years. This discrepancy may be due to a relatively small sample size in Chiu et al.’s research as compared to our study.

Investigating the cumulative effect of multiple allergens, we found that sensitization to more than one perennial allergen significantly increases the prevalence of allergic rhinitis and asthma. On the contrary, Agache and Ciobanu [22] showed that polysensitization to seasonal pollens was a risk factor for asthma in children with seasonal allergic rhinitis.

The main limitation of our study was its retrospective design. We evaluated data from the patients’ medical documentation, which could have partly influenced the accuracy of our results. Another limitation is a relatively wide range of the study subjects’ age (from 6 – 18 years). However, age did not change the goodness-of-fit of the multivariate models. Therefore, subgroup analyses were less reasonable. We evaluated data from the medical documentation of patients from an allergy clinic; thus, it is possible that our study population was skewed. However, all patients participating in this study were under regular care of allergy specialists from our clinic, including physical examination, lung function measurements, and other necessary tests, which exclude any doubts concerning the heterogeneity of diagnostic procedures.

In conclusion, we showed that sensitization to the seasonal allergens timothy or birch as well as to the perennial allergens house dust mite or cat is associated with asthma and allergic rhinitis in children. Our study determined the role of multiple perennial indoor allergens in the development of allergic diseases in children. The identification of the specific allergens makes them potential targets for intervention and prevention strategies. Thus, our findings could be an additional reason to consider an early introduction of immunotherapy in children sensitized to the above allergens.

References

[1] O’Connell EJ. The burden of atopy and asthma in children. Allergy. 2004; 59 (Suppl 78): 7-11. CrossRef PubMed

[2] Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. CMAJ. 2009; 181: E181-E190. CrossRef PubMed

[3] D’Amato G, Cecchi L, D’Amato M, Liccardi G. Urban air pollution and climate change as envi-

| Number of sensitizing allergens: | No AR | AR | OR⁴ | 95% CI | p |
|--------------------------------||-------||-----|------|-------|
|                                | N     | %  | N   | %    |      |
| **Perennial**                  |       |    |     |      |      |
| Non                            | 3,003 | 77.3 | 575 | 48.2 |      |
| One                            | 306   | 7.9 | 173 | 14.5 | ref  |
| Two                            | 362   | 9.3 | 258 | 21.6 | 1.26 | 0.99 | 1.61 | 0.0644 |
| Three and more                 | 213   | 5.5 | 186 | 15.6 | 1.54 | 1.18 | 2.03 | 0.0017 |
| **Seasonal**                   |       |    |     |      |      |
| Non                            | 1,918 | 71.8 | 372 | 40.6 |      |
| One                            | 191   | 7.1 | 109 | 11.9 | ref  |
| Two                            | 167   | 6.3 | 121 | 13.2 | 1.27 | 0.91 | 1.77 | 0.1585 |
| Three and more                 | 396   | 14.8 | 315 | 34.4 | 1.29 | 0.96 | 1.84 | 0.0592 |

⁴Dependent variable – diagnosis of allergic rhinitis; ref – reference category; AR = allergic rhinitis.
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[1] Cullinan P, MacNeill SJ, Harris JM, Moffat S, White C, Mills P, Newman Taylor AJ. Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. Thorax. 2004; 59: 855-861. CrossRef PubMed

[2] Celedon JC, Litionjua AA, Ryan L, Platts-Mills T, Weiss ST, Gold DR. Exposure to cat allergen, maternal history of asthma, and wheezing in first 5 years of life. Lancet. 2002; 360: 781-782. CrossRef PubMed

[3] Hesselmar B, Aberg N, Åberg B, Eriksson B, Björksten B. Does early exposure to cat or dog protect against later allergy development? Clin Exp Allergy. 1999; 29: 611-617. CrossRef PubMed

[4] Remes ST, Castro-Rodriguez JA, Holberg CJ, Martinez FD, Wright AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. J Allergy Clin Immunol. 2001; 108: 509-515. CrossRef PubMed

[5] Chiu CY, Huang YL, Tsai MH, Tu YL, Hua MC, Yao TC, et al. Sensitization to food and inhalant allergens in relation to atopic diseases in early childhood: a birth cohort study. PLoS One. 2014; 17: e9102809.

[6] Agache I, Ciobanu C. Risk factors and asthma phenotypes in children and adults with seasonal allergic rhinitis. Phys Sportsmed. 2010; 38: 81-86. CrossRef PubMed

[7] von Mutius E. Month of birth and allergic disease at the age of 7-10 is associated with airway hyperresponsiveness and atopic asthma by age 11-14. PLoS One. 2014; 9: e98878. CrossRef PubMed

[8] von Mutius E, Becker AB, Köyzer SK. Exposure to Beta-(1,3)-D-glucan in house dust at age 7-10 is associated with airway hyperresponsiveness and atopic asthma by age 11-14. PLoS One. 2014; 9: e98878. CrossRef PubMed

[9] McPhee T, Katz IR, reonment risk factors of respiratory allergy: an update. J Investig Allergol Clin Immunol. 2010; 20: 95-102, quiz 102. PubMed

[10] Devereux G. The increase in the prevalence of asthma and allergy: food for thought. Nat Rev Immunol. 2006; 6: 869-874. CrossRef PubMed

[11] Schaub B, von Mutius E. Obesity and asthma, what are the links? Curr Opin Allergy Clin Immunol. 2005; 5: 185-193. CrossRef PubMed

[12] Burke W, Fesinmeyer M, Reed K, Hampson L, Carlsten C. Family history as a predictor of asthma risk. Am J Prev Med. 2003; 24: 160-169. CrossRef PubMed

[13] Erbas B, Lowe AJ, Lodge CJ, Matheson MC, Hosking CS, Hill DJ, Vicendese D, Allen KJ, Abramson MJ, Dharmage SC. Persistent pollen exposure during infancy is associated with increased risk of subsequent childhood asthma and hayfever. Clin Exp Allergy. 2013; 43: 337-343. CrossRef PubMed

[14] Garner R, Kohen D. Changes in the prevalence of asthma among Canadian children. Health Rep. 2008; 19: 45-50. PubMed

[15] From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2012. Available from: http://www.ginasthma.org/. [Cited 2013 March 26]

[16] Boument J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier T, Akdis CA. Changes in the prevalence of asthma and allergic rhinitis: I. Single-center experience. J Investig Allergol Clin Immunol. 2010; 20: 1392-1397. CrossRef PubMed

[17] Dik N, Dold S, Reitmeir P, Stiepel M, von Mutius E. Family history as a predictor of asthma in early life. Chest. 2004; 126: 869-874. CrossRef PubMed

[18] Kohen D, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Lancet. 2000; 356: 1392-1397. CrossRef PubMed

[19] Dik N, Tate RB, Manfreda J, Anthonisen NR. Risk of physician-diagnosed asthma in the first 6 years of life. Chest. 2004; 126: 1147-1153. CrossRef PubMed

[20] Yoshida K, Adachi Y, Akashi M, Itazawa Y, Murakami Y, Odajima H, Ohyu Y, Asakawa A. Cedar and cypress pollen counts are associated with the prevalence of allergic diseases in Japanese schoolchildren. Allergy. 2013; 68: 757-763. CrossRef PubMed

[21] Maheswaran D, Zeng Y, Chan-Yeung M, Scott J, Osornio-Vargas A, Becker AB, Köyzer SK. Exposure to Beta-(1,3)-D-glucan in house dust at age 7-10 is associated with airway hyperresponsiveness and atopic asthma by age 11-14. PLoS One. 2014; 9: e98878. CrossRef PubMed

[22] Luc S, Ili S, Sommerfeld C, Bürgmann R, von Mutius E, Wahn U; Multicentre Allergy Study Group. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Lancet. 2000; 356: 1392-1397. CrossRef PubMed