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Eijsink, P.E.D.

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Chapter 8

Early and late sensitization and the likelihood of developing asthma at the age of six

P.E.D. Eysink, G. ter Riet,
R.C. Aalberse, P.J.E. Bindels

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Abstract

Aim To determine whether children with late onset sensitization are at the same risk of developing asthma at the age of six as children sensitized early in life (<4 years).

Methods 545 children, aged 1-3, visiting their GPs for coughing (>5 days), were tested for IgE antibodies by RAST. The IgE positive (12.3%) and a random sample of the IgE negative (<0.5 U/ml) children were followed up to the age of 6 when the asthma status was established. Children were defined as early onset (positive response <4 years of age), late onset (≥4 years) or never sensitizers.

Main outcome measure Asthma at the age of 6 (combination of both symptoms and/or use of asthma medication, and impaired lung function).

Results 28 of 96 children (29%) had been diagnosed with asthma: none of the late onset sensitizers had developed asthma at the age of 6, 12% of the never sensitizers and 64% of the early sensitizers. The risk of developing asthma at the age of six was significantly higher for the early onset children than for the late or never sensitizers, whose risks were similar. This was also found in strata of family history of atopy and infantile eczema.

Conclusion Early sensitization (<4 years of age) as shown by RAST, is an important risk factor for the development of asthma at the age of six. Late onset sensitizers were at a similar risk as the never sensitizers. The latter children can be treated less aggressively because a diagnosis of asthma is not to be expected in the short term. Preferably, this relation should be studied in a larger study as the group of late onset sensitizers was very small.

Introduction

According to international consensus [1-3], asthma in children younger than 6 years of age is predominantly a clinical diagnosis, based on the presence of recurrent coughing and wheezing. Furthermore, in the majority of chil-
children over two with asthma, allergies play an important role [4,5]. However, in the Dutch guidelines for General Practitioners [3] allergy testing in children under 4 is not recommended, because, it is said, an allergy can seldom be detected and a negative test does not rule out that a child will become positive in the future. Other international guidelines do not mention age-dependent allergy testing in relation to asthma [1,2,6,7]. However, in most guidelines it is acknowledged that atopy is a clear risk factor both for the persistence of bronchial hyperresponsiveness and for symptoms of asthma [8,9]. Furthermore, among infants and young children who suffer from wheezing with viral infections, allergy or family history of allergy is the factor most strongly associated with continuing asthma through childhood [5].

Several studies [9-11] indicated that children who were sensitized early in life (defined as either sensitization before the age of two [10], before the age of eight [11] or before the age of 10 [9]) were at a higher risk of developing asthma than children with late-onset sensitization. Knowing the relation between the age of seroconversion and the risk of asthma may be of clinical relevance and might shed light – be it indirectly – on the (immunological) mechanisms behind the development of asthma.

The aim of this study is to determine whether children with late onset sensitization are at the same risk of developing asthma at the age of six as children sensitized early in life (<4 years).

Patients and Methods

Selection of the study population

Between 1995 and 1997, general practitioners in the Netherlands included one to three year old children in a study on the development of inhalation allergy and asthma. Children with complaints of coughing for at least the
previous five days and their parents visiting their GPs were invited to participate and informed consent was obtained from the parents. At baseline, data on age, gender and geographical region were collected. Furthermore, the parents completed a structured questionnaire with 11 questions on duration of coughing, presence of atopy in the family, breast-feeding, infantile eczema, smoking by parents and contact with pets. A blood sample was obtained from the children and total IgE and specific IgE for cat, dog and house dust mite were determined. The IgE positive children were matched to IgE negative children in each of the 12 strata defined by age (3 categories of one year), gender and region (urban vs. rural). At the age of six, the children were invited for a lung function measurement at the clinic, to determine the child’s asthma status. At that time, parents completed two questionnaires on their child’s asthma and allergic symptoms [12,13] and a blood sample was obtained. The study was approved by the Medical Ethics Committee of the Academic Medical Center, University of Amsterdam.

**Laboratory methods**

Total IgE and allergen-specific IgE were determined as described earlier [14]. In brief: blood, obtained by finger prick and adsorbed on filter paper, was eluted. Assays for measuring total serum IgE and specific IgE were adjusted for the application of small amounts of plasma. Total IgE was expressed in international units per millilitre (IU/ml), RAST results were expressed in RAST units per millilitre (U/ml, one RAST unit representing approximately 2.4 ng of specific IgE [15]). All test results were corrected for actual amounts of plasma used in the tests, using serum albumin as a reference protein.

**Lung function measurements and histamine challenge**

The FEV₁ was measured with a Pulmoassist 2 spirometer (Jaeger, Wurzburg, Germany). Values for the FEV₁ are those of Zapletal et al [16]. On the same day, bronchial histamine challenge tests were performed with a gauged DeVilbiss 646 nebulizer (DeVilbiss, Somerset, MA, USA) with an
output of 0.13 ml/min according to the modified method of Cockcroft et al [17]. A 0.9% phosphate-buffered saline solution and doubling histamine concentrations from 0.03 to 16 mg/ml, were inhaled for two minutes during tidal breathing with the child’s nose clipped. FEV₁ was measured 30 and 90 seconds after each inhalation until FEV₁ had fallen by at least 20% from the initial value. The provocation concentration of histamine which induced a 20% fall in FEV₁ (PC₂₀) was calculated from a log-dose response curve.

**Data analysis**

*Independent variables*

The results of the RAST were dichotomized as IgE negative or IgE positive. IgE positivity to cat, dog and/or house dust mite was defined as $\geq 0.5$ U/ml. Early sensitization was defined as a positive response before the age of 4 to any of the tested allergens, and late sensitization was defined as a positive response to any of the allergens after the age of 4. Thus, a child could be defined as: 1) never sensitized, 2) late-onset sensitized (sensitization $\geq$4 years), and 3) persistent early-onset sensitized (sensitization $<$4 years).

*Dependent variables*

Asthma was defined as a combination of both symptoms and/or use of asthma medication, and impaired lung function. **Symptoms** were defined as: current complaints or complaints during the previous 12 months of wheezing and/or shortness of breath and/or recurrent coughing. In addition, use of asthma medication was defined as use of $\beta_2$-agonists or inhaled corticosteroids currently or during the previous 12 months. **Impaired lung function** was defined as a positive histamine test, defined as PC₂₀ $<$8 mg/ml.

All children who had not experienced any symptoms during the previous years and had not used asthma medication were not invited for lung function measurement and were designated as non-asthmatics.
Statistical analyses

χ² tests were used to compare prevalences between groups. Logistic regression analysis was used to analyze the association between the different patterns of sensitization and the outcome of asthma at the age of 6. These models were also used for the analysis of the influence of various potential risk factors (e.g. family history of atopy, infantile eczema) on becoming asthmatic.

Data analysis was performed with SPSS 10.0 for Windows.

Results

During the inclusion period, 545 one to three year old children were eligible. 134 of them were selected to participate in the second part of the study. However, twenty-six children did not attend the lung function test or had an insufficient technique, so we had 26 missing values on asthma. Furthermore, for another 12 (11.2%) children it was not possible to determine whether they were early, late or never sensitizers, because they did not have a second blood sample or it was unknown whether they had converted before or after the age of 4. None of these 12 children had been diagnosed with asthma. Thus, a total of 96 children were available for descriptive analyses with respect to the development of asthma: 58 (60.4%) of them were never sensitized, 5 (5.2%) were sensitized after the age of 4 (late onset sensitizers), and 33 (34.4%) were persistent early onset sensitizers. The early sensitized children had higher levels of total IgE both at baseline and at the age of 6 (P < 0.001) compared with the never and late onset sensitizers. No significant differences were found in total IgE at baseline and at the age of 6 between the never and the late onset sensitizers. No significant differences were found in the type of sensitization between the early onset and late onset sensitizers.

Of the 96 children, 28 (29.2%) had been diagnosed with asthma. The prevalence of asthma at the age of 6 for the three groups showed that none of the
late onset sensitizers had developed asthma at the age of 6, whereas 7/58 (12.1%) never sensitized children and 21/33 (63.6%) early sensitized children had. The early onset sensitized children were at a significantly higher risk of being asthmatic at the age of six (OR = 14.0, 95% CI = 4.8-40.3) than the children never being sensitized, whereas the late onset sensitizers were at a similar risk for asthma compared with the never sensitizers (OR = 0.6, 95% CI = 0.1-2.9).

Comparing the prevalences of becoming asthmatic in strata of family history of allergy for pollen, for animals or house dust mite, showed that the risk of becoming asthmatic was significantly higher for the early onset sensitizers compared with the never sensitizers and late onset sensitizers. This was also found for a positive or negative family history of asthma and in strata of children with and without infantile eczema.

Discussion

We found that sensitization to inhalant allergens early in life (defined as sensitization before the age of 4) was a strong risk factor for the development of asthma at the age of 6. In contrast, children who became sensitized at or after the age of 4 (late onset) were at a similar risk for developing asthma at the age of 6 as the children who had never been sensitized. Thus, children who were not sensitized before the age of 4 had a low risk of developing asthma at the age of 6. This was irrespective of whether they were sensitized after the age of four. Thus, in the short term i.e. until the age of six, no diagnosis for non-sensitized children is to be expected. Therefore, the GP can treat these young non-sensitized children less aggressively and on a basis of watchful waiting. Of course, it is still possible that these children develop asthma at a later age, say ten years, but that is as yet unknown (and beyond the purpose of our paper).
There are some limitations to this study. Firstly, we had a small number of children in our study, especially in the group of late onset sensitizers. Secondly, for a number of children it was not possible to determine whether they were late, early onset or never sensitizers. As it turned out, none of these children were diagnosed with asthma. If all these children were late onset sensitizers, the percentage of late onset sensitizers with asthma would still be 0% (from 0/6 to 0/20). If these children were all early onset sensitizers, this would affect the percentage of early onset sensitizers developing asthma in the sense that it would decrease from 64% (21/33) to 47% (21/45). However, the risk of developing asthma at the age of 6 is still significantly higher for the early onset than for the never and late onset sensitizers. A third limitation is that the children were included into the study at different ages (one to three). The older children therefore, have ‘survived’ for a longer period of time and thus it is plausible that fewer three year olds than one and two year olds developed asthma at the age of six. However, all negative one and two year olds were tested around their third or fourth birthday for another study and the results of these blood samples were taken if appropriate. Furthermore, the children who were indeterminable, were not entered into the analyses, and none of them had developed asthma at the age of six.

The results of our study are in line with other studies [9-11,18,19], which indicated that sensitization is an important determinant of the subsequent development of asthma; RRs up to 10 for the risk of asthma in allergic children have been reported.

Furthermore, several studies [9-11,20] indicated that children who were sensitized to aero-allergens early in life are at a higher risk of developing asthma than children with late-onset sensitization. However, in these studies, among other differences, the cut-points for early versus late seroconversion were two, eight, and ten years of age respectively. It is difficult to obtain more IgE determinations from young children, which forces investigators to select a convenient cut-point for the age of conversion. We chose the age of four as a cut-point because of the Dutch asthma-guidelines
[3] (in which the age of four is also the cut-point), and limitations in our data. Ideally speaking, the relation between early sensitization and asthma would be studied within a study protocol using (often) repeated specific IgE determinations and continuous monitoring of the presence of asthma. More realistically, a final asthma diagnosis would be established at a certain age, say 12.

In summary, we found that sensitization to aero-allergens before the age of 4 is a risk factor for the subsequent development of asthma at the age of 6 in contrast to sensitization after the age of 4. As a diagnosis of asthma is not expected in the short term, late-onset (and non-) sensitized children can be treated less aggressively. Nevertheless, the relation between early and late sensitization and asthma should be studied in a larger study, as the group of children who became sensitized after their fourth birthday was very small in our study.

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References

