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Children with Chronic Asthma Have a Significant Sensitization to Multiple Aeroallergens: A Prospective Study in 74 Children

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Abstract

Background: Recent evidence suggests that exposure to high levels of allergen during early life might contribute to the increasing prevalence of allergic disease. A high incidence of Der p allergen was found in early infancy as a risk factor for developing asthma.

Materials and Methods: We have randomly recruited 37 children with chronic asthma (CA) and 37 with episodic asthma (EA) and evaluated clinical manifestations, skin prick tests (SPT), RAST and spirometry results. All children were studied at baseline and at three-month intervals. The follow-up was 12 months. Informed consent was obtained from parents of each child. Data were analysed with the X^2-test.

Results: We report the significant differences between CA and EA children. CA children had in addition, compared to EA children significant early onset of symptoms, delayed diagnosis, and poorer spirometry results.

Discussion: Among the significant results, we stress that positive family history is as always a potent determinant of atopy. A strong influence of environmental factors on the development of severe asthma is demonstrated by the significant prevalence in the CA children of maternal smoke during pregnancy, parental smoke, damp houses, and viral infections. While the prevalence of bottle-feeding corresponds to an equal number of breastfed children in either group, we emphasize that a substantial difference is the greater number of CA children sensitized to multiple inhalant allergens.

Introduction

Several authors consider pediatric asthma a disease to be cured and not to be prevented, thus they only cite the prevention of environmental allergens, the basic treatment of pediatric asthma [1]. Allergy to inhaled allergens is presently a common complaint during infancy and childhood, and exposure may even occur as early as prenatally. Personal analyses have shown that 12% of infants and children suffer from asthma, and 15% from allergic rhinitis, and the cumulated incidence in adolescents varies between 25-35%, while the prevalence is about 20%. What is not appreciated by several colleagues is that the onset of such disorders is increasingly in advance, with growing numbers of wheezing infants at an early age (allergic marsh) [2]. Although the relationship between atopy (positive SPT and/or RAST) and bronchial asthma has been suggested for long time only in the recent years this relationship has been established [1,2]. It has been shown that both the severity of asthma and bronchial hyper responsiveness (BHR) [3-6] correlate with the degree of atopic sensitization [7-12]. In addition it has been shown that the amount of aeroallergen present in the environment and the degree of atopy as measured by the number and size of SPT responses, are all factors that may interact to increase the risk of asthma [13,14] and of BHR [15-18]. Chronic allergen exposure may result in the release of mediators, the development of local inflammatory reactions and clinical symptoms. On the other side, several reports indicate an ongoing increase in the incidence, prevalence and severity of atopic diseases both in industrialized and developing countries [19]. Allergy to inhaled allergens is presently a common complaint during infancy and childhood, and exposure may even occur as early as prenatally [1]. A recent analysis has shown that 12% of infants and children suffer from asthma, 15% from allergic rhinitis, and the cumulated incidence in adolescents varies between 25-35%, while the prevalence is about 20% [20]. Der p appears to be the most common offending allergen in asthma [21], and an early exposure to this allergen is associated with a significant increase of the risk of asthma at the age of 11 [22]. Hence, the "increased exposure to dust mites and other indoor allergen may be a factor contributing to the recent increases in the morbidity and mortality associated with asthma" [22]. Moreover the exposure during the 2 first year of life to environmental tobacco smoke and home dampness was found more frequently found among the house dust-mite sensitized children than among the controls [23]. In a prospective study on 1167 infants [24] it was demonstrated that some environmental factors such as maternal smoking, lower social classes, were interdependent and had a profound effect on the prevalence of asthma but not on other allergic disorders During the last decade, great interest has been devoted to prevent the development of allergy and asthma in these children [20] We have studied the atopic status and the severity of asthma in a group of asthmatic children to investigate the influence of atopy and environmental factors on the clinical course of asthma.

Materials and Methods

We have prospectively studied two groups of 37 children affected with chronic or episodic asthma followed at the Allergy and Immunology Division, Department of Pediatrics, University of Rome "La Sapienza". According to international guidelines [25,26], we define CA children as those who frequently have nocturnal symptoms in all seasons, decrease of PEF, exercise induced asthma and other signs of BHR. CA children despite adequate treatment control their asthmatic symptoms only with continuous multiple medications, including prophylaxis with inhaled ß2-bronchodilators and topical steroids (and uncommon use of oral steroids). EA children have cough and wheeze on an intermittent basis, and control their symptoms with preventative drugs, theophylline and bronchodilators on a when needed basis. In both group we evaluated the following parameters: personal and family history of allergy; SPTs; atopic status; spirometry data.

We determined the history of allergic symptoms such as atopic dermatitis (AD), asthma and allergic rhinitis in first-degree relatives (parents and siblings). Moreover, we have studied whether AD were present before or contemporary to asthma. The lung function of each child was measured with a Printer II Spirometer (Markos, Monza, Italy). We evaluated FEV1, FVC, PEF, FEV1/FVC index, FEF25-75. Informed consent was obtained from parents of each child.

Skin prick test

Appropriate emergency equipment and medications were available on site. Parents were required to discontinue all oral/topical corticosteroids during the trial, antihistamines for 7 days, and all ß-agonists for 12 hr before SPT application. Skin testing was done at baseline by the prick method by a doctor trained in allergy with the co-operation of a qualified nurse. The skin was marked with a ballpoint pen for the allergens to be tested. The babies were then tested with: histamine hydrochloride (1 mg/ml) as a positive control and isotonic saline as a negative control. We continued with a battery of inhalant allergens, including Dermatophagoides pteronyssinus, Alternaria alternata, Lolium perenne, Olea europea and Parietaria officinalis (SARM, Roma, Italy). The diagnostic extract of each individual allergen was placed on the volar surface of the forearm as drops through which the skin was superficially pricked with a straight pin for one second. A new pin was used for each prick test and then discarded, and the drop of the extract was then wiped off about one minute after the prick [27].

SPTs were read 20 minutes after the test was finished and considered positive as follows:

+ when the wheal was the half of the histamine wheal;

++ when the wheal was equal to the histamine wheal;

+++ when the wheal was two-fold the histamine wheal;

++++ when the wheal was more than two-fold the histamine wheal [28].

We took for positive only children with a wheal ^{3} 3 mm with an area = 7 mm2 (cut-off) So we considered as positive only the children with a mean wheal diameter of 3 mm or larger than the negative (saline) control. A positive (histamine) control was performed to ensure the absence of any antihistamine drug interference [28,29].

Total IgE

The determination of the total serum IgE level was done by paper radioimmunosorbent test (PRIST, Pharmacia Diagnostics AB, Sweden), and results were expressed in International Units per ml. Specific IgE antibodies and determination of specific IgE levels by radioallergosorbent test (Phadezym RAST, Pharmacia Diagnostics).

RAST results are expressed in »RAST Units« as follows:

1st class = IgE levels<0.35 IU/ml,

2nd class = IgE levels>0.35 IU/ml and lesser than 0.7 IU/ml,

3rd class = IgE levels between 0.7 IU/ml and 17 IU/ml,

4th class = IgE levels higher than 17 IU/ml.

Only RAST results>0.35 IU/ml were considered positive. The statistical calculations were performed using the X2 test and Student T test.

Results

Clinical features of asthmatic children are summarized in Table 1 and SPT and RAST results in (p=0.02 and p=0.006, respectively, for CA children vs EA children). SPT and RAST results related to multiple sensitizations are summarized (p=0.0021 for CA children vs EA children). No significant differences were found between the two groups in sex-distribution, personal atopy and breast-feeding, whereas family history of atopy was highly statistically significant. Figures 1 and 2 show the mean incidence of asthmatic symptoms and related treatment, and the results of pulmonary function testing, respectively.

No statistically significant difference was found in the two groups in the type of allergens and in the size of the SPT reactions. However 32/37 (86%) children with CA and 22/37 (59%) children with EA had positive SPT responses to two or more allergens (p=0.0086).

The geometric mean of total serum IgE was 258.29 IU/ml (range 1-1000) in the CA group and 259.36 UI/ml (range 21-1500) in the EA group (NS).

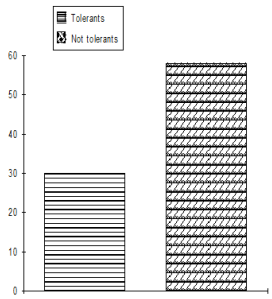

Figure 1: Asthma development in 74 children.

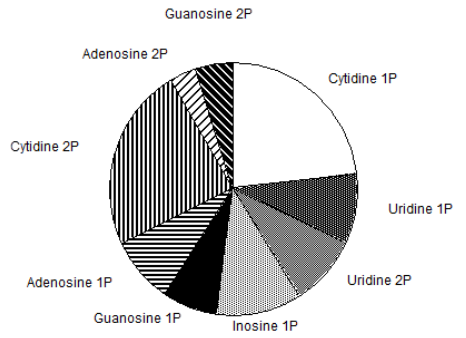

Figure 2: Nucleotide content of breast milk Mean of 2, 4, 8 e 12 weeks of breastfeeding, values are expressed in µmol/l1P, 2P=mono- di-phosphate.

In the group with CA and in the group of EA the median age of the onset of the symptoms was 1 year (1-11 yrs) and 3 years (1-14 yrs) respectively (p=0.0013); the median age at the first visit to our Clinic was 6 years (1-14 yrs) and 5 years (1-14 yrs), respectively. The period elapsed between the onset of asthma and the first visit to our Clinic was of 5 years and 3 years respectively (p=0.012).

Discussion

In this study we report that multiple sensitizations to environmental allergens is significantly associated to CA. Actually 86% of children with CA had more than one positive SPT response whereas the prevalence in the EA group was 59% (p=0.0086). These highly significant difference in the rate of multiple sensitized children with CA compared to the EA group appears to be critical. since being affected with more than one sensitization seems to be important prognostic worsening, especially when seasonal allergens are associated As reported by other authors [8-10], there is a strict relationship between grading of asthma and grading of atopy. It has been suggested that continuous exposure to environmental allergens induced a continuous release of mediators with a chronic inflammatory process in the airways, such as the basis for BHR.

Many studies have demonstrated the relationship between allergens exposure and BHR [15-19]. Furthermore, the elimination of aeroallergens could decrease BHR [17].

Tolerance	Children With Tolerance (N° 31)	Children Without Tolerance (N°43)
Age of ad onset (median)	3 mos p<0.0059 mos (1 mos-5 yrs)	p<0.005 (2 mos-3 yrs)
Age of the first examination (Median)	2 yr 8 mos (4 mos-10 yrs 7 mos)	2 yrs 9 mos (6 mos-4 yrs 10 mos)
Age of development of tolerance (Median)	4 yrs (2-9 yrs)	
Age of the last follow up (Median)	6 yrs 5 mos (4 yrs 2 mos–14 yrs)	7 yrs 2 mos (4 yrs 3 mos-9 yrs 10 mos)

Table 1: Clinical features of asthmatic children.

This study also demonstrates that children with CA have a younger age at the onset of the symptoms and higher at the first visit to our Clinic. Possibly, the absence of environmental controls and of preventive therapy could favor the atopic march and increase the severity of asthma. In addition, we suggest that children with multiple sensitization should be considered at risk of CA; moreover this risk is higher if they are not well treated, as it possible in a specialized clinic. Therefore, according to previous and recent studies, prevention of atopic diseases in predisposed newborn babies, is worthwhile [30].

In this cohort of 74 children, was completely neglected as usually [19] or disregarded [31] the issue of specific immunotherapy (SIT). We have recently demonstrated that 27/29 (93.1%) controlled studies in 2.077 children and as many controls have shown the effectiveness of SIT in pediatric age in the treatment of asthma due to pollens, house dust mites (Der p), epidermal derivatives, and molds (p<0.0001) [10]. In all studies the children of the control groups, were treated with the available, appropriate drugs, and cared for by their doctors as the children of the study group. Therefore 93% of the studies have confirmed the SIT's positive influence on the natural history with a total remission of asthmatic symptoms in the children that regularly completed the SIT cycle [32]. In addition severe adverse reactions during SIT are almost non-existent in children [33].

The Der p allergen is certainly the most common offending allergen in asthma [5], and early exposures to Der p are associated with a significant increase of the risk of asthma at the age of 11 [22]. In a recent study on over 1000 children followed up for 18 years [34] the strongest predictor for childhood atopy, BHR, and asthma symptoms was family history, also associated with substantial exposure to passive smoke, as in our study. This study confirms and extend the report that exposure during the 2 first years of life to environmental tobacco smoke and home dampness are more frequently found among the Der p sensitized children than among the controls [23]. A prospective study on 1167 infants [24] added among the environmental factors the maternal smoking (during pregnancy statistically significant, and lower social classes had a profound effect on the prevalence of asthma.

Environmental and dietary manipulations should be addressed to "high-risk babies" in order to avoid, or postpone the risk of sensitization, or to mitigate the clinical course of the atopic disease once established. On the portal of our Clinic stands an inscription suggesting a great responsibility: "In puero homo" ("In infant is the seed of the future man") since this may also mean that our goal should be to transmit to the adult the fruit of our preventive measures, an organism free of atopy, thus insuring the best quality of life both to infants, children and adults [1].

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