

Exposure to a high concentration of mite allergen in early infancy is a risk factor for developing atopic dermatitis: A 3-year follow-up study

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The cause of allergy is multi-factorial, and the development of an allergic disease seems to be the result of an interaction between genetic and environmental factors. The goal for preventing the development of allergic diseases is to avoid sensitization to allergens. The aim of this work was to study whether or not exposure to environmental allergens early in infancy would influence the occurrence of various allergic diseases in later life. On an annual basis, a total of 931 healthy newborns were followed-up until they reached 3 years of age. The occurrence of allergic diseases was recorded by trained medical students during visits. Measurement of *Dermatophagoides pteronyssinus* (Der p 1) concentration in house dust was performed when each baby was 18 and 36 months old. Total and specific immunoglobulin E (IgE) antibodies against Der p 1, cow's milk, and egg white were evaluated at birth and at 18 months of age. The following results were obtained: at 3 years of age, 10.4% had bronchial asthma (BA), 21.4% atopic dermatitis (AD), 7.0% urticaria, and 46.8% had experienced wheezing; higher family allergy scores led to a higher incidence of AD ($p=0.0012$); exposure to a mite allergen concentration of 1 $\mu\text{g/g}$ of dust may be associated with a higher incidence of AD ($p=0.0156$); the presence of Der p 1 IgE antibody at 18 months of age was associated with a higher incidence of BA ($p=0.0001$); and children sensitized to egg whites at 18 months of age had an increased risk of developing AD at 3 years of age ($p=0.0187$). Hence, early exposure to mite allergen is a risk factor for the development of atopic dermatitis, but seems not to be related to the development of bronchial asthma. Early sensitization to egg whites increases the risk of developing AD. The early detection of serum Der p 1 IgE antibody is associated with a higher incidence of bronchial asthma.

**Jing-Long Huang¹,
Chih-Chang Chen², Ming-Ling Kuo¹
and Kue-Hsiung Hsieh¹**

¹Division of Allergy, Asthma and Rheumatology, Department of Pediatrics, Chang Gung Children's Hospital and Chang Gung University, Taoyuan, ²Department of Pediatrics, Taipei Municipal Children's and Maternal Hospital, Taipei, Taiwan

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Jing-Long Huang, M.D., Division of Allergy, Asthma and Rheumatology, Department of Pediatrics, Chang Gung Children's Hospital, 5 Fu-Hsing Street, Kweishan, Taoyuan 333, Taiwan
Tel.: +886-3-328-1200
Fax: +886-3-328-8957
E-mail: long@adm.cgmh.com.tw

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In recent years, a substantial body of evidence has shown an increasing prevalence of allergic diseases in both industrialized (1,2) and developing countries (3). The cause of allergy is multi-factorial, and the development of an allergic disease seems to be the result of an interaction between genetic factors and several environmental factors. The environmental factors include potential allergens, inhalant as well as food allergens, and possible adjuvant factors that may facilitate sensitization.

The prevalence rates of the 10 leading pathologic conditions in the United States show that 'allergies' rank second in order after dental problems and are among the most costly health problems resulting in morbidity, hospitalization, and mortality (4). Therefore, a world-wide effort has been made to identify the risk factors involved in the development of allergic disease, to surcease the prevalence of allergic diseases all over the world.

In this work, we report on the environmental factors that affect the occurrence of various

allergic diseases in 931 general population-based newborns followed-up from birth to 3 years of age.

Subjects and methods

Pregnant women who visited the prenatal care clinics of five medical centers in Taipei city during a 6-month period from October 1992 to March 1993 were contacted by trained medical students. Approval of the study was given by the ethical committee of all hospital authorities involved. Mothers (and fathers if available) were interviewed. The study was fully explained, and informed consent was obtained. Premature newborns or newborns with major health problems were not included. A total of 5400 healthy newborns were enrolled. Information was obtained regarding the gender of the newborn, family allergy score (FAS), type of feeding, passive exposure to smoking, and the presence of pets in the home. The FAS score (5) was based on whether or not bronchial asthma (BA), atopic dermatitis (AD), and allergic rhinitis (AR) were present in other family members. The highest FAS score was 13. A FAS score of ≥ 3 was defined as a high-risk group, and 0 as a low-risk group. Blood samples were obtained from umbilical cords of 2178 newborns and by venepuncture from 374 babies at 18 months of age. Total immunoglobulin E (IgE) was measured by using the Pharmacia IgE CAP assay (Pharmacia A.B., Uppsala, Sweden). Specific IgE antibodies against the house dust mite *Dermatophagoides pteronyssinus* (Der p 1), cow's milk, and egg whites were measured by using the CAP RAST FEIA Fluoroimmunoassay (Pharmacia A.B.).

House dust was collected twice, once when the infant was 18 months of age (282 samples) and once when the child reached 3 years of age (789 samples). Dust samples were collected from three sites in the home: the mattress of the subject, the bedroom floor, and the lounge. Dust collection was performed according to a modified Tovey's method, using a portable vacuum cleaner (6). Dust samples were collected for 2 min from a 1-m² area at each site. After collection, the samples were preserved at -20 °C until they were analyzed. Der p 1 concentration in the house dust was measured by using an enzyme-linked immunosorbent assay (ELISA), as reported previously (6).

The clinical symptoms and signs of BA, AR, AD, and urticaria were explained to mothers (and fathers if available) by medical personnel (trained medical students and nurses) during the prenatal care clinics. During the questionnaire surveys (7) at 6 months and 2 years of age, the clinical symp-

toms and signs of each disease were described in detail, and answers were re-confirmed by medical personnel by telephone. The diagnosis of infantile asthma was made according to the reports of Tabachnik et al. (8) and Martinez et al. (9). In brief, a diagnosis of asthma required three or more separate episodes of wheezing that showed a good response to bronchodilator therapy. Wheezing ever was defined as the patient having had a wheezing episode during the follow-up period. AD was diagnosed on the basis of the nature of skin lesions, their typical distribution, recurrence, and pruritus (10). As stated above, as many as possible of the babies when 18 months of age were directed back to hospitals for physical check-ups by physicians and for blood collection. Home visits were also made by medical students when the children reached 3 years of age. The kappa statistics for the diagnosis of BA, AD, and urticaria between the questionnaire and the physicians was 0.95, 0.92, and 0.9, respectively. As the kappa statistic for AR was 0.6, the data was not used for analysis.

Statistical analysis

Chi-square tests or Fisher's tests were used, where appropriate, to compare categorical data among different groups. A p-value of ≤ 0.05 was considered to be significant. Kappa statistics were computed to examine the agreement of diagnosis of the various allergic disorders between the questionnaire and the physicians.

Results

The total number of newborns enrolled into this study following birth was 5400; 1649 were evaluated (by questionnaire) at 6 months of age; 1003 (by hospital visit) at 18 months of age; 809 (by questionnaire) at 2 years of age; and 931 (by home visit) at 3 years of age. It is important to note that the parents of high-risk infants (i.e. FAS ≥ 3) were more co-operative than those of low-risk infants, as reflected in the gradually increasing follow-up rate of the high-risk group, e.g. 18.0% at birth and 24.9% at 3 years of age ($p < 0.01$).

As expected, the incidence of allergic diseases increased as the children grew older (Fig. 1). The incidence of BA at the age of 6 months and 3 years was 2.4% and 10.4%, respectively ($p = 0.001$); for AD was 15.9% and 21.4%, respectively ($p = 0.007$); and for urticaria was 2.1% and 7.0%, respectively ($p = 0.02$). Babies with a FAS of ≥ 8 had a greater incidence of AD than those without family atopy (38.9% vs. 19.3%, $p = 0.0012$), but there was no effect on the incidence of BA (16.9%

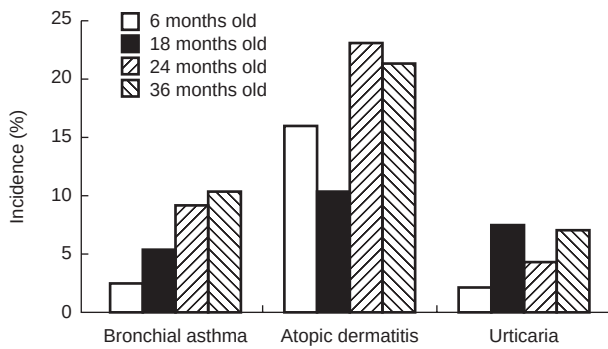


Fig. 1. The incidence (number of patients divided by the total number of children in the follow-up) of bronchial asthma (BA), atopic dermatitis (AD) and urticaria increased as the children grew older.

vs. 9.7%, $p=0.333$) or urticaria (13.6% vs. 6.7%, $p=0.233$).

A cord blood IgE concentration of greater than 1 IU/ml was found to increase the chance of developing BA (15.4% vs. 5.3%, $p=0.041$, Table 1), but there was no effect on the incidence of AD or urticaria. Interestingly, the total serum IgE level at 18 months of age showed no significant influence on the incidence of allergic diseases (Table 1), although 18-month IgE levels were influenced by cord blood IgE levels (data not shown).

The effect of exposure to the house dust mite allergen Der p 1 on the incidence of allergic diseases is shown in Table 2. When 1 µg/g of Der p 1 in fine dust was used as the cut-off point, the babies exposed to 1 µg/g of Der p 1 tended to be affected more often by AD than those exposed to <1 µg/g of Der p 1 (21.6% vs. 5.3%, $p=0.0156$).

The relationships between sensitization to the allergen Der p 1, cow's milk, or egg whites at 18 months of age and the occurrence of allergic diseases were also studied (Table 3). A CAP RAST value of greater than class I was considered as sensitized. Sensitization to Der p 1 increased the risk of developing BA (26.6% vs. 10.0%, $p=0.0001$). Sensitization to egg whites increased the risk of developing AD (33.8% vs. 20.3%, $p=0.0187$), but sensitization to Der p 1 at 18 months of age did not increase the risk of developing AD (26.6% vs. 21.6%, $p=0.353$).

Discussion

Studies recording the evolution of disease from birth over a period of time are often marred by a gradual loss of subjects. The parents of high-risk infants were more co-operative than those of low-risk infants, as reflected by the gradually increasing follow-up rate for the high-risk group. The increasing incidence of allergic diseases with age in this study could be a result of selection bias towards children with higher heredity scores, but the analysis of data of 931 children over the 3-year study period could provide some important information, such as risk factors for the development of various allergic diseases.

Despite rapid progress in the knowledge of pathogenesis of allergic diseases and the development of new anti-allergic drugs, the prevalence, morbidity, and mortality resulting from BA continue to rise. As the development of allergy results from an interaction between genetic factors and environmental factors, enormous effort has been attempted world-wide to identify the genetic markers of susceptibility and to manipulate the environmental factors (both acting directly or as adjuvants).

AD is a common skin disease that affects 10–20% of the population, usually with onset during infancy. The frequency of AD appears to have increased over the past three decades. Although a parental history of AD appears to be the most valuable predictive parameter, avoidance of relevant trigger factors can modify the development of AD (11). The current aim is to prevent triggering in those susceptible persons (especially during the early stages of life) and the development of sensitization, which leads to allergic diseases, in particular AD, in later life.

The heredity of allergic diseases has been confirmed by carefully conducted genetic studies (12). Many studies in different countries have shown that between 50 and 75% of all patients with allergies have a positive family history of allergic diseases. Tariq et al. studied 1218 children and showed that a positive family history doubled the risk of asthma and quadrupled the risk of rhinitis, but there was a lack of association between family history of atopy and eczema after infancy (13).

Table 1. Cord blood immunoglobulin E (IgE) and total serum IgE (at 18 months of age) and the occurrence of allergic diseases at 3 years of age

	Cord blood			Total serum IgE at 18 months of age		
	≥ 1 IU/ml (n=26)	<1 IU/ml (n=190)	p-value	<180 IU/ml (n=291)	≥ 180 IU/ml (n=70)	p-value
Bronchial asthma	4 (15.4%)	10 (5.3%)	0.0414	36 (12.4%)	13 (18.6%)	0.1739
Wheezing ever	16 (61.5%)	102 (53.7%)	0.4506	144 (49.5%)	36 (51.4%)	0.7702
Atopic dermatitis	8 (30.7%)	50 (26.3%)	0.6308	61 (21.0%)	21 (30.0%)	0.1052
Urticaria	2 (7.7%)	10 (5.3%)	0.6120	18 (6.2%)	5 (7.1%)	0.7856

Table 2. Exposure to house dust mite *Dermatophagoides pteronyssinus* (Der p 1) and the occurrence of allergic diseases at 3 years of age

	≥ 1 µg/g of dust (n=760)	<1 µg/g of dust (n=38)	p-value
Bronchial asthma	84 (11.1%)	3 (7.9%)	0.7892
Wheezing ever	363 (47.8%)	14 (36.8%)	0.1882
Atopic dermatitis	164 (21.6%)	2 (5.3%)	0.0156
Urticaria	56 (7.4%)	1 (2.6%)	0.5120

The results of our study show that babies with a higher FAS had a much higher chance of developing AD ($p=0.0012$) than those without a family history of atopic disease. This therefore confirms previous studies which show that a family history of allergy is a risk factor for development of allergies.

The importance of cord blood IgE in predicting the development of allergies is still controversial. Several factors may contribute to its less-than-perfect reliability, including sensitivity of the measurement, choice of cut-off point, and selection of the study population. While Businco et al. (14), Casimir et al. (15), Croner et al. (16), and Michel et al. (17) found determination of cord blood IgE a valuable predictor for allergy development, in contrast, Hansen et al. (18), Varonier et al. (19), and Ruiz et al. (20), reported no value. Tariq et al. (13) reported that a high serum IgE level at birth was a risk factor for eczema and allergen sensitization but that it was a poor predictor for the development of atopic disease. In this study, we found that a cord blood IgE concentration of ≥ 1 IU/ml was a good predictor for development of BA at 3 years of age ($p=0.0414$), but not a good predictor for development of AD ($p=0.631$). Total serum IgE at 18 months of age, although influenced by cord blood IgE (data not shown), showed no effect on development of atopic disease. The genetic risks for the development of atopic disease may not necessarily be the same as those for allergen sensitization.

Most asthma in children and young adults is characterized by the presence of specific IgE antibodies against a wide variety of aeroallergens. The clear evidence that atopy is inherited (13), its association with human leukocyte antigen (HLA)

types (21,22), and its tentative localization to chromosome 11q (23), emphasizes the importance of genetic factors in predisposing people to allergic disease. However, the induction of IgE antibody formation depends on exposure to the antigen. In Taiwan, Der p 1 is the most predominant house dust mite (24,25). When compared to 25% of healthy children, more than 90% of asthmatic children were found to be sensitive to Der p 1 (26,27). In this study therefore, the magnitude of exposure to the house dust mite Der p 1 was compared with the development of mite-specific IgE antibody, because measurement of Der p 1 in house dust can give an index of the concentration of mite antigen (24). Several reports (28–30) have shown that exposure to 2 µg/g of Der p 1 increase the risk of specific sensitization in atopic children and young adults and thus may facilitate allergic airway diseases. Beck & Korsgaard (31) reported that exposure to a higher level of house dust mites corresponds to a relative risk of 4.6 and a clear dose–response relationship between exposure and disease activity of AD. The present study revealed that babies exposed to ≥ 1 µg/g of Der p 1 tended to develop AD more frequently than those exposed to <1 µg/g of Der p 1. This suggests that the threshold exposure level of dust mites in AD is lower than in BA.

Exposure to high levels of dust mite can be a confounding variable indicating special lifestyle habits that are associated with a higher prevalence of AD. The method of feeding, passive smoking, social class, season of birth, room temperature, humidity, infections, and exposure to pets can influence the expression of phenotypes of atopic diseases. This might explain the fact that exposure

Table 3. Presence of *Dermatophagoides pteronyssinus* (Der p 1), cow's milk, and egg white specific immunoglobulin E (IgE) antibody at 18 months of age and the occurrence of allergic disease at 3 years of age

	Der p 1			Cow's milk			Egg white		
	<0.35 IU/ml* (n=282)	≥ 0.35 IU/ml* (n=79)	p-value	<0.35 IU/ml* (n=219)	≥ 0.35 IU/ml* (n=142)	p-value	<0.35 IU/ml* (n=295)	≥ 0.35 IU/ml* (n=65)	p-value
Bronchial asthma	28 (10%)	21 (26.6%)	0.0001	25 (11.4%)	24 (16.9%)	0.1371	39 (13.2%)	10 (15.4%)	0.6451
Wheezing ever	148 (52.5%)	32 (40.5%)	0.0599	109 (49.8%)	71 (50.0%)	0.9662	149 (50.3%)	31 (47.0%)	0.6810
Atopic dermatitis	61 (21.6%)	21 (26.6%)	0.3533	48 (21.9%)	34 (24.0%)	0.6536	60 (20.3%)	22 (33.8%)	0.0187
Urticaria	19 (6.7%)	4 (5.1%)	0.5902	14 (6.4%)	9 (6.3%)	0.9834	20 (6.8%)	3 (4.6%)	0.7791

*IgE antibody ≥ 0.35 IU/ml=CAP class I.

to a high concentration of mites can increase the incidence of AD rather than BA.

Sensitization is the prerequisite for the occurrence of atopic diseases. However most previous studies on the occurrence of IgE antibodies in children have been cross-sectional (32,33). Only a few studies have addressed the relationship between sensitization and the appearance of atopic disease over many years (34,35). In this study, we measured the specific IgE antibodies against house dust mites (Der p 1), cow's milk, and egg whites in 18-month-old babies and followed-up to monitor the appearance of various allergic diseases at 3 years of age. We found that the presence of mite IgE antibody increased the prevalence of BA ($p=0.0001$), whereas egg white IgE antibody increased the prevalence of AD ($p=0.0187$). These results are consistent with a report by Sigurs et al. (36), which noted that IgE antibodies in children are usually associated with current or later atopic disease. Therefore, preventing early exposure and sensitization is a very important step for decreasing the rising prevalence of allergic disease, especially for the 'at-risk' group.

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