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Original Article

Prospective study of atopic status in infants of the cohort in Tokyo, Japan

Tsutomu Iwata,[1] Hiroshi Hayakawa,[1] Fusako Komoda,[1] Masae Koseki,[3] Tatsuko Miyakawa,[3] Toyoo Sakurayama,[3] Kaeko Yamasaki,[3] Michie Honjou,[4] Noriko Hirakawa,[4] Kazuko Inoue,[5] Naohiro Hohashi[2] and Chieko Sugishita[2]

[1]Department of Pediatrics, Mejirodai Campus, and [2]Department of Family Nursing, Faculty of Medicine, University of Tokyo, [3]Department of Public Health and Health Centre, Office of Bunkyo-District, [4]Department of Pediatrics, Second Hospital of Tokyo Women's Medical College and [5]Department of Pediatrics, Tokyo Metropolitan Hiroo Hospital, Tokyo, Japan

ABSTRACT

Several risk factors for the development of allergic diseases are considered including, for example, the level of IgE in cord blood or in the peripheral blood of neonates and the antigenic effect of some foods that are ingested by both babies and mothers during pregnancy and during the lactation period. However, not all infants with atopic diathesis develop allergic diseases. To clarify the risk factors and the mechanism for developing allergic diseases, particularly bronchial asthma (BA), we prospectively investigated atopic diatheses and symptoms in children in a cohort using a questionnaire method. The factors correlated to development of allergic diseases, as a whole, at the age of 5–6 years were atopic family history and any allergic symptom at 4 months of age. However, not all subjects with atopic dermatitis developed BA later on. High levels of total IgE and positive IgE antibody against egg white were not risk factors for developing BA at the age of 5–6 years.

Key words: atopic dermatitis, atopy, bronchial asthma, cohort study, infants, risk factor.

Correspondence: Dr Tsutomu Iwata, Department of Pediatrics, Mejirodai Campus, Faculty of Medicine, University of Tokyo, 3-28-6 Mejirodai, Bunkyo-ku, Tokyo 112, Japan. Email: <iwped-tky@umin.u-tokyo.ac.jp>

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INTRODUCTION

Several risk factors for the development of allergic diseases are considered including, for example, the level of IgE in cord blood[1,2] or in the peripheral blood of neonates[3] and the antigenic effect of some foods that are ingested by both babies and mothers during pregnancy and during the lactation period.[4,5] However, not all infants with atopic diathesis develop allergic diseases. It is important to prospectively follow infants in a cohort and to evaluate the frequency of allergic diseases in order to clarify the risk factors and mechanism for developing allergic diseases, particularly bronchial asthma (BA).

Bunkyo-ku is one of 23 administrative districts in Tokyo, Japan. Its population is approximately 170 000 and there are approximately 1000 births/year. In the present paper we describe a prospective study performed over 5–6 years in the Bunkyo-ku area to evaluate allergic risk factors that may induce chronic atopic dermatitis (AD), BA or other allergic diseases.

METHODS

Since 1989, we have implemented a special health care plan for identifying any risk factor for the development of allergic diseases. A total of 1212 infants have visited the local health centre for a physical examination of their health and developmental condition at 4 months of age from April 1989 until March 1990. A group of these infants (group A) was selected for further examination and care due to their suspected allergic symptoms and/or

a family history of atopy. A subset of group A infants (group A-1) was further selected to undergo blood tests to analyze their atopic backgrounds. Group A-2 consisted of infants who were physically examined and were seen by pediatric allergologists, but who did not undergo blood tests. Group B consisted of infants who received ordinary health care service alone because of their non-atopic status.

Blood tests were performed on infants at 6 months or younger and included a complete blood test (CBC), an eosinophil count and total serum IgE (by radioimmunosorbent test; RIST) and specific IgE antibody (by radioallergosorbent test; RAST) to, for example, anti-egg white, cows' milk, soy bean and so on, depending on the individual case.

A questionnaire was mailed to a total of 942 children who lived in the Bunkyo-ku area in December 1994 to determine whether they had allergic diseases when they were 5–6 years of age. The criteria of the diagnosis for allergic diseases are as follows: (i) AD, diagnosed by a doctor within the past year or the child having chronic itchy eczema with a typical distribution or lichenification or fissure of the ear; (ii) BA, diagnosed by a doctor as having asthma or asthmatic bronchitis within the past year or, if not diagnosed by a doctor, diagnosed by complaints of more than two episodes of wheezy and dyspneic attacks within the past 3 months; (iii) allergic rhinitis (AR), diagnosed by a doctor within the past year; (iv) allergic conjunctivitis (AC), diagnosed by a doctor within the past year; (v) gastrointestinal allergy, diagnosed by a doctor within the past year or the child having episodes of diarrhea and/or abdominal pain after taking specific foods within the past 3 months; and (vi) urticaria, diagnosed by a doctor within the past year.

Statistical analyses were performed by the Chi-squared test with Yates' correction. Sensitivity (positive concordance rate) and specificity (negative concordance rate) were calculated using the following formulae:

$$\text{Sensitivity (\%)} = A \times 100/(A + B)$$
$$\text{Specificity (\%)} = D \times 100/(C + D)$$

where A, B, C and D are numbers as given by the representative Table 1.

RESULTS

Four hundred and ninety-one subjects (male 242, female 249) replied to the questionnaire. Groups A (subgroups A-1 and A-2) and B were divided as described in the Methods; namely, group A consisted of 139 subjects (group A-1 61; group A-2 78) and group B consisted of 352 subjects. The frequency of allergic diseases was calculated depending on the diagnostic criteria described in the Methods. These results are summarized in Table 2. Atopic dermatitis was found in 84 of 491 subjects (17.1%). When the frequency of AD was compared between group A-1 (or group A) and group B, the difference was highly significant ($P < 0.0001$). The frequency of BA in group A-1 was also significantly higher than in group B ($P < 0.01$). The frequency of other allergic diseases was not significantly different between groups A and B.

A family history of allergic diseases within second-degree relatives was assessed for all 491 subjects on the basis of answers to the questionnaire. If answers were not able to be assessed, the charts for each child that had been written at the time of the physical examination at 4

Table 1.

	+	−
+	A	B
−	C	D

Table 2. Frequency of allergic diseases in children 5–6 years of age

	Group A			Group B	Sum
	A-1	A-2	A (A-1 + A-2)		(groups A + B)
AD*	23 (37.7%)	16 (20.5%)	39 (28.1%)	45 (12.8%)	84 (17.1%)
BA†	13 (21.3%)	5 (6.4%)	18 (13.0%)	32 (9.1%)	50 (10.2%)
AR	8 (13.1%)	8 (10.3%)	16 (11.5%)	28 (8.0%)	44 (9.0%)
AC	6 (9.8%)	2 (2.6%)	8 (5.8%)	8 (2.3%)	16 (3.3%)
GIA	1 (1.6%)	0 (0%)	1 (0.7%)	3 (0.9%)	4 (0.8%)
U	3 (4.9%)	3 (3.8%)	6 (4.3%)	9 (2.6%)	15 (3.1%)
Total	61 (100%)	78 (100%)	139 (100%)	352 (100%)	491 (100%)

*$P < 0.001$ (Chi-squared test with Yates' correction) †$P < 0.01$ (Chi-squared test with Yates' correction).

For a definition of groups, refer to Methods. AD, atopic dermatitis; BA, bronchial asthma; AR, allergic rhinitis; AC, allergic conjunctivitis; GIA, gastrointestinal allergy; U, urticaria.

and/or 18 months of age were referred to to find accurate records regarding family histories. Of 491 subjects, 288 did not have a family history of atopy and 203 did. Seventy-five children had a family history of atopy only on the paternal side, 94 children had a family history of atopy only on the maternal side and 34 children had a family history of atopy on both parental sides. We compared the frequency of allergic diseases in children at 5–6 years of age in groups of children who had a family history of atopy on one parental side alone as well as those that had a family history of atopy on both parental sides with the group of children who did not have a family history of atopy. In children who had a family history of atopy on the paternal side, there were significantly more allergic diseases as a whole than in the group of children who did not have a family history of atopy (Table 3). In children who had a family history of atopy on the maternal side, there were significantly more cases of BA and allergic diseases as a whole than in the group of children who did not have a family history of atopy (Table 4). There was no significant difference in the frequency of allergic diseases in children who had a family history of atopy either on the maternal or the paternal side (data not shown).

We compared the frequency of allergic diseases in children at 5–6 years of age with that in the same children at 4 months of age on the basis of records of the physical examination of the children (Table 5). Of 130 children who had displayed symptoms of any allergic disease at 4 months of age, 33 (25.4%) had AD at 5–6 years of age. In contrast, 51 of 361 subjects who had no evidence of allergic disease at 4 months of age had AD at 5–6 years of age. This difference was highly significant ($P < 0.01$). Of the 130 subjects who had evidence of allergic disease at 4 months of age, 20 (15.4%) had BA at 5–6 years of age, while in the group of children without any atopic history at 4 months of age, there was a significantly lower frequency of BA at 5–6 years of age ($P < 0.05$). Finally, subjects with evidence of allergic disease at 4 months of age had significantly more allergic diseases as a whole at 5–6 years of age than did subjects who did not have a history of atopy at 4 months of age ($P < 0.05$). Subjects with eczema (probably AD) at 4 months of age showed

Table 3 Allergic diseases and the family history of atopy on the paternal side

Allergic diseases at 5–6 years of age	Family history of allergic diseases	
	Yes	No†
Atopic dermatitis		
Yes	16	39
No	59	249
Bronchial asthma		
Yes	9	21
No	66	267
Any allergic diseases*		
Yes	26	65
No	49	223

†No allergic family history on either the paternal or the maternal side.
*$P < 0.05$ (Chi-squared test with Yates' correction).

Table 4 Allergic diseases and the family history of atopy on the maternal side

Allergic diseases at 5–6 years of age	Family history of allergic diseases	
	Yes	No†
Atopic dermatitis		
Yes	20	39
No	74	249
Bronchial asthma*		
Yes	15	21
No	79	267
Any allergic diseases*		
Yes	32	65
No	62	223

†No allergic family history on either the paternal or the maternal side.
*$P < 0.05$ (Chi-squared test with Yates' correction).

Table 5 Frequency of allergic diseases at 4 months and 5–6 years of age

Allergic diseases at 5–6 years of age	Allergic diseases at 4 months of age	
	Yes ($n=130$)	No ($n=361$)
Atopic dermatitis**		
Yes	33 (25.4%)	51 (14.1%)
No	97 (74.6%)	310 (85.9%)
Bronchial asthma*		
Yes	20 (15.4%)	30 (8.3%)
No	110 (84.6%)	331 (91.7%)
Allergic rhinitis		
Yes	13 (10.0%)	31 (8.6%)
No	117 (90.0%)	330 (91.4%)
Allergic conjunctivitis		
Yes	6 (4.6%)	10 (2.8%)
No	124 (95.4%)	351 (97.2%)
Gastrointestinal allergy		
Yes	0 (0%)	4 (1.1%)
No	130 (100%)	357 (98.9%)
Acute urticaria		
Yes	5 (3.9%)	10 (2.8%)
No	125 (96.2%)	351 (97.2%)
Any allergic diseases*		
Yes	48 (36.9%)	89 (24.7%)
No	82 (63.1%)	272 (75.3%)

*$P < 0.05$, **$P < 0.01$ (Chi-squared test with Yates' correction).

significantly more AD at 5–6 years of age ($P < 0.01$); however, subjects with wheezing at 4 months of age did not show any increased tendency to have BA at 5–6 years of age (data not shown).

The normal value of serum IgE has a wide range of variation when measured by RIST. In Japan, the geometric mean value of serum IgE for infants below 6 months of age has been reported to be 3.8 IU/mL.[6] In 1989, the lower limit of detection of serum IgE was 10 IU/mL when it was measured by commercial laboratories using RIST (technical report by the Special Reference Laboratory, Japan). Therefore, we tentatively settled on 10 IU/mL IgE as the concentration used to divide group A-1 into two: (i) those subjects who had ≥ 10 IU/mL IgE were considered to be part of the high-IgE group; and (ii) those with <10 IU/mL IgE were considered to be part of the low-IgE group. In group A-1, 37 subjects had ≥10 IU/mL serum IgE and were classified as part of the high-IgE group. Twenty-three subjects with <10 IU/mL IgE were classified as the low-IgE group. There was no significant difference in the frequency of AD and BA at 5–6 years of age between the high- and low-IgE groups (Table 6).

In group A-1, 24 subjects had positive IgE antibody against egg white (RAST class ≥2). Subjects in group A-1 were divided into two groups: (i) those with positive IgE RAST to egg white; and (ii) those with negative RAST. There was no significant difference in the frequency of AD and BA at 5–6 years of age between the positive and negative RAST groups (Table 7).

Table 6 Comparison of the frequency of allergic diseases at 5–6 years of age and total IgE levels at less than 6 months of age

Allergic diseases at 5–6 years of age	Total serum IgE levels ≥ 10 IU/mL	< 10 IU/mL
Atopic dermatitis*		
Yes	15	7
No	22	16
Bronchial asthma†		
Yes	5	8
No	32	15

*$\chi^2=0.264$, $P=0.6071$ (with Yates' correction); †$\chi^2=2.631$, $P=0.1048$ (with Yates' correction).

Table 7 Comparison of the frequency of allergic diseases at 5–6 years of age and the positivity of specific IgE antibody to egg white at less than 6 months of age

Allergic diseases at 5–6 years of age	Specific IgE antibody to egg white (RAST score) ≥2	<2
Atopic dermatitis*		
Yes	10	13
No	14	24
Bronchial asthma†		
Yes	3	10
No	21	27

*$\chi^2=0.062$, $P=0.8040$ (with Yates' correction); †$\chi^2=1.079$, $P=0.2989$ (with Yates, correction).

Discussion

Atopy is a genetically determined diathesis. Several studies have been performed to research the so-called atopic gene. One British group has reported that an atopic gene is located at chromosome 11q137.[7] Another group in the US has shown the important role of chromosome 5q in relation to the segregation of genes that code many cytokines, such as interleukin (IL)-3, IL-4, IL-5 and granulocyte macrophage-colony stimulating factor (GM-CSF).[8] However, it is not clear what the risk factor(s) is for developing allergic disease, even among subjects with atopic diathesis, and also whether infants with AD are determined to develop BA. It is worthwhile to follow up infants in the same district to establish whether they develop any allergic diseases over time.

We used a questionnaire survey to determine the frequency of allergic diseases in children 5–6 years of age who were living in an urban district of Tokyo, Japan. All children who responded to the questionnaire had been physically examined by pediatricians at 4 months of age and were divided into two groups (A and B) according to their physical status and/or family history of allergy. Infants classified as group A were asked to undergo another physical examination by pediatric allergologists because of their symptoms and/or family history of atopy. Furthermore, 61 infants (designated as group A-1) were analyzed for peripheral eosinophils, total serum IgE and specific IgE antibodies to major allergens when they were 4–6 months of age because they had clearer symptoms of allergy and/or a family history of atopy compared with other members of groups A (designated as group A-2) and B. Of 491 children at 5–6 years of age, 84 were reported to have AD (17.1%). This ratio is compatible to results of a recent epidemiological survey performed by the Study Group of the Ministry of Health and Welfare, Japan.[9] Of 491 subjects, 10.2% of children had BA at 5–6 years of age. This ratio is slightly higher than that determined by the Study Group survey, which reported a frequency of BA of 5.4 and 6.4% in younger and school children, respectively.[9] The difference is probably due to the fact that subjects in the present study were from a residential area in Tokyo. In general, children from an urban area

show a greater tendency to have BA than do children from rural area.[10]

Subjects in group A-1 showed significantly more morbidity of BA and AD than did subjects in group B, meaning that subjects in group A-1 who had any allergic symptoms at 4 months of age and/or had a family history of atopy are atopic at 5–6 years of age. Infants with atopic diathesis are thought to present with AD first and develop BA later. This phenomenon is called the 'allergic march'.[11] This imaginable term has been recently accepted by people in Japan. Parents, who have babies with atopic diathesis (mainly eczema) feel burdened that their baby will develop BA. However, the concept of the allergic march is not fully verified as our data show that infants with eczema at 4 months of age showed a significantly increased tendency to have AD but not BA at 5–6 years of age. In addition, infants with wheezy episodes at 4 months of age did not have a significant tendency to develop BA at 5–6 years of age. Taken together, these data indicate that not all infants with allergic symptoms at 4 months of age inevitably develop BA. However, infants with any allergic symptoms at 4 months of age showed a significantly greater tendency to have an allergic disease at 5–6 years of age and infants with a family history of atopy are predicted to develop allergic diseases later. As far as the amount of total IgE is concerned, it was not a predictive factor for allergic diseases, as infants with ≥10 IU/mL IgE did not have a greater tendency to develop allergic diseases at 5–6 years of age. The positivity of specific IgE antibody against egg white was also not a predictive factor for allergic diseases at 5–6 years of age, although infants with positive RAST to egg white showed a higher frequency of allergic diseases at 1.5 years of age compared with infants with negative RAST (T Iwata *et al.*, unpubl. obs., 1994).

Sensitivity and specificity were calculated to assess and compare the predictive values of different factors. The sensitivity was rather low, ranging from 28.6 to 41.7%, and the specificity ranged from 75.1 to 82.0%. The parameter that showed the highest sensitivity for BA was a positive maternal family history of atopy. However, it is not feasible to conclude that a positive maternal family history is the best predictive factor for the development of asthma.

It is important to know more precisely the mechanisms responsible for the development of allergic diseases and to research and dissect environmental factors as well as other genetic factors that contribute to the development of allergic diseases.

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