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A Study of the Factors Responsible for the Development of Allergic Diseases in Early Life

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SUMMARY In order to analyze the determinants involved in the development of allergic diseases early in infancy, we examined the environmental and genetic factors that might affect the induction of such diseases during infancy, using a questionnaire. Maternal pharyngitis during pregnancy was significantly related to the development of atopic dermatitis in their progeny. Moreover, the frequency of the maternal infection was associated with a significantly increased risk of allergy in their infants. The prevalence of post-delivery maternal allergy was positively linked to the allergic symptoms in their children while the likelihood of bearing allergic children was related to the numbers of allergic individuals within their family. These results suggested that pre- and post-natal maternal factors and any genetic predisposition might modify the development of allergy in infancy.

The increased prevalence of allergic diseases in recent years may be the result of alterations in lifestyle and the reduced exposure to infectious diseases during infancy as suggested by the hygiene hypothesis.[1] In addition to the factors relating to early infancy, prenatal maternal factors may also affect the development of allergies in an offspring as has been suggested by the presence of allergen-sensitized T lymphocytes as early as 22 weeks into the gestation period.[2] The present study was performed to illustrate the factors relating to the development of allergies during the initial two years of infancy based on a questionnaire covering pre- and post-natal history and environmental factors.

MATERIALS AND METHODS

Subjects

This study included 207 children consisting of 108 males and 99 females, aged one to two years, who visited the pediatric clinics at the Yokohama Red Cross Hospital, JR Sendai Hospital, Toho University Ohmori Hospital, Tokyo Medical and Dental University, Kitasato University, and National Minami-Fukuoka Chest Hospital in Japan. Of these 207 children, 45 (21.7%) had atopic dermatitis and 22 (10.6%) had bronchial asthma. Ten (4.8%) had both of them.

Methods

Questionnaire

The mothers, that were capable of understanding and answering the detailed questionnaire

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from the International Study of Asthma and Allergies in Childhood (ISAAC)[3] and the U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis,[4] were asked about their maternal history both during the pregnancy and child-bearing periods, any childhood history of diseases, vaccinations, feeding, as well as about the environment of the children, and any family history of allergic diseases. We used the ISAAC 2002 with only slight modifications especially for background elements of the environmental factors.

Diagnosis of the childhood allergic diseases

The diagnosis of atopic dermatitis was made by physical examination by a pediatrician according to the Hanifin and Rajka criteria.[5] Typical morphology and distribution such as facial and extensor involvement and chronic or chronically relapsing dermatitis were two important criteria. Two other factors, early age of onset and personal or family history of atopy, were omitted, because they were not useful for young children in this study. Similarly, children experiencing recurrent wheezing episodes confirmed by a medical record were diagnosed as having asthma by a pediatrician based on the criteria of the American Thoracic Society.[6]

Statistical analysis

A comparison of the factors that may be responsible for the development of allergy was made between allergic and non-allergic children using χ^2 test with Yates' correction (when necessary), and Spearmann correlation coefficients as appropriate. Logistic regression analysis was performed to select infectious symptoms during pregnancy significantly associated with the development of allergy. All p values less than 0.05 were defined as significant.

RESULTS

Influence of maternal infections during pregnancy on the development of allergy in their infants

Among the infectious symptoms of the mothers during pregnancy, maternal fever was significantly associated with allergic symptoms in their children that consisted of atopic dermatitis and asthma (Chi = 4.3878, $p < 0.05$). Similarly, maternal cough was associated with the development of asthma (Yates Chi = 5.9107, $p < 0.05$). However, in both cases, logistic regression analysis revealed that there were no significant associations between them. Therefore we concluded that they showed weak relevancy. Maternal pharyngitis was associated with the development of atopic dermatitis (Yates Chi = 4.417, $p < 0.05$) (Fig. 1) and this was confirmed by the results of the logistic regression analysis ($p < 0.05$). In the questionnaire, we recorded the time of the appearance of the respective symptoms, but it showed no significant association with the childhood allergy.

Furthermore, the frequency of the maternal infections, including diarrhea, fever, rhinorrhea, cough, pharyngitis, bronchitis and pneumonia, dur-

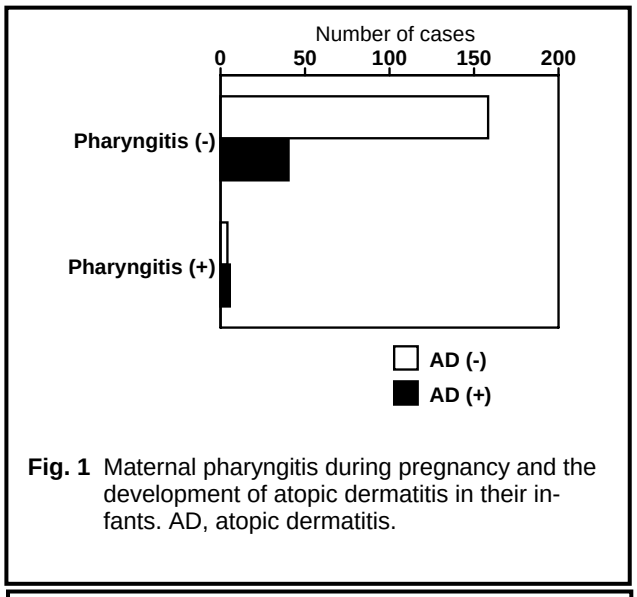

Fig. 1 Maternal pharyngitis during pregnancy and the development of atopic dermatitis in their infants. AD, atopic dermatitis.

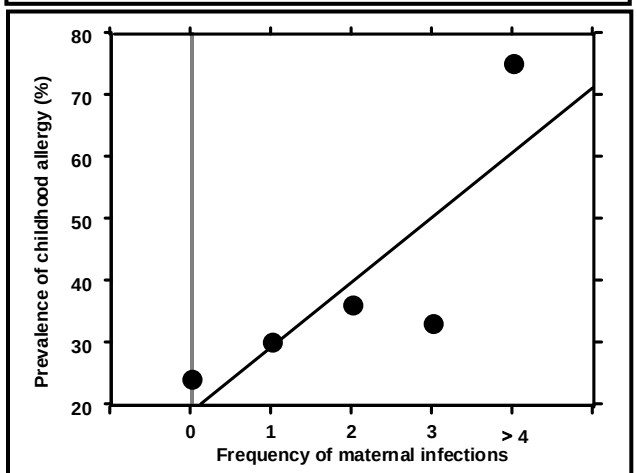

Fig. 2 A correlation between maternal infections during pregnancy and the prevalence of allergic diseases in the offspring.

ing pregnancy closely paralleled the prevalence of allergic diseases in the offspring (r = 0.82299, p < 0.01) (Fig. 2).

Relationship between maternal allergy during pregnancy and the development of allergy in their offspring

The childhood incidence of allergic diseases, including both atopic dermatitis and asthma, differed significantly based on the allergic symptoms of their mothers during pregnancy (Yates Chi = 49.6, p < 0.01). Furthermore, childhood allergy prevailed as the number of maternal allergic symptoms increased with a strong link between them (rs = 0.955921, p < 0.01). Specifically, the incidence of atopic dermatitis in isolation correlated with these symptoms (rs = 0.955921, p < 0.01), rather than asthma in isolation (Fig. 3). In this analysis, the numbers of maternal allergic symptoms were defined as the numbers of the allergic diseases consisting of bronchial asthma, atopic dermatitis, allergic rhinitis, Japanese pollinosis, allergic conjunctivitis, urticaria, and food allergy, as evidenced by the description of the findings by the allergologists.

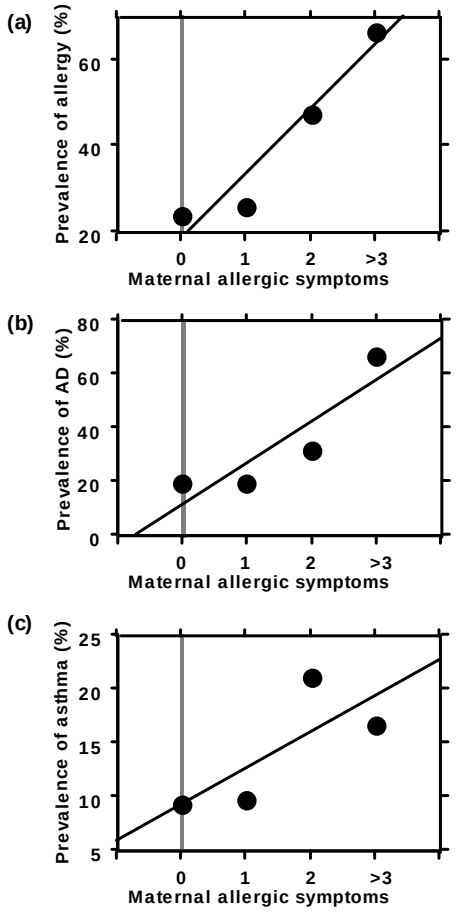

Fig. 3 The prevalence of infantile allergy and the number of allergic symptoms in the mothers during pregnancy. The rate of development of total childhood allergy including atopic dermatitis and asthma (a) and that of atopic dermatitis in isolation (b) but not that of asthma in isolation (c) correlated with the frequency of the maternal allergic signs. AD, atopic dermatitis.

Association of maternal allergic symptoms after delivery with the allergy in their children

In addition to maternal allergies during pregnancy, maternal allergic diseases during the child-bearing period appeared to lead to a markedly increased prevalence of allergy in their progeny (p < 0.01) (Fig. 4). Similarly, the numbers of maternal allergic symptoms after childbirth significantly paralleled the prevalence of the sum of allergic diseases (both atopic dermatitis and asthma) (rs = 0.985658, p < 0.01), atopic dermatitis in isolation (rs = 1, p < 0.01), and asthma in isolation (rs = 1, p < 0.01) (Fig. 5).

Relationship of allergic diseases in the infants to those of their family members

The childhood incidence of allergic diseases (rs = 1, p < 0.01), either in individuals with atopic dermatitis plus asthma, or atopic dermatitis in isolation (rs = 1, p < 0.01), or asthma in isolation (rs

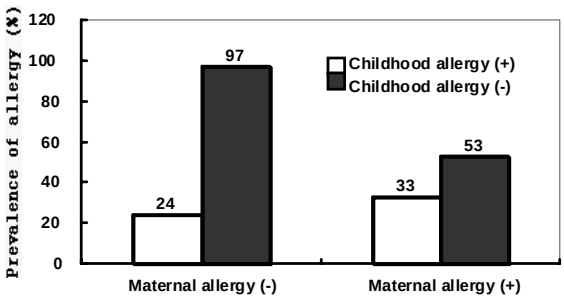

Fig. 4 The influence of maternal allergy during the childhood-bearing period on the prevalence of allergy in their progeny. Open columns and closed columns indicate children with and without allergy, respectively.

= 1, $p < 0.01$) was strongly linked with the numbers of the allergic individuals in their families (Fig. 6).

Influence of infectious diseases early in life on the development of allergy in the children

Based on the results of the questionnaire regarding the diagnosis and the time of the childhood respiratory infectious diseases, no childhood infectious respiratory diseases in isolation had any influence on the prevalence of allergic diseases (data not shown).

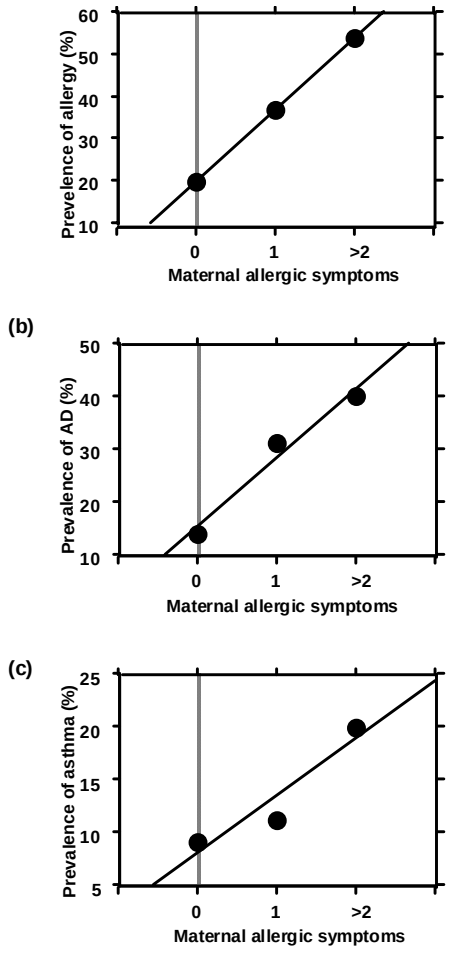

Fig. 5 Correlations of the rate of development of infantile allergy with the number of the allergic symptoms in their mothers. The prevalence of atopic dermatitis plus asthma (a) and that of atopic dermatitis in isolation (b), but not that of asthma in isolation (c) paralleled the maternal allergy. AD, atopic dermatitis.

Association between the nutrition and allergic signs in the infants

The feeding of the children, which was either breast or cows milk, irrespective of the duration, did not affect the development of allergy (data not shown).

Prevalence in the onset of allergic diseases in regard to vaccinations

The prevalence of childhood allergy did not differ among the groups that received DPT, BCG vaccination, polio, measles, rubella, varicella, mumps, or influenza virus vaccinations (data not shown). The effect of immunizations for diphtheria

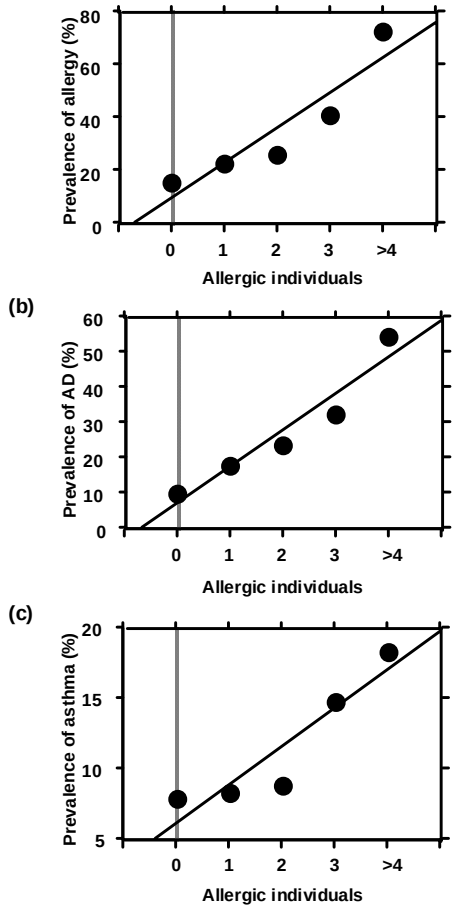

Fig. 6 Significant correlations between childhood allergy and a family history of allergy. The development of atopic dermatitis plus asthma (a), that of atopic dermatitis in isolation (b), and that of asthma in isolation (c) was influenced by the number of patients experiencing allergy in the family. AD, atopic dermatitis.

and tetanus (DT) or for the Japanese encephalitis virus could not be assessed due to the small numbers of such cases.

Influence of indoor pets on the allergic symptoms

The presence or absence of pets, either in the prenatal or the postnatal period, and the duration of their exposure, especially cats and dogs, had no influence on the allergic symptoms in the children (data not shown).

Association of environmental tobacco smoke and allergy in the children

The homes of smokers or nonsmokers did not affect allergy in their infants. And the development of childhood allergy was not changed by the time of exposure and the extent of any smoking (data not shown).

DISCUSSION

Previous studies have depicted several factors that might be related to the development of childhood allergy, such as nutrition, environments with the presence of mites, cats and tobacco, different lifestyles including the occupation and the economic status, any genetic predisposition and infantile infections. These may represent potential determinants.[7,8] In addition to the above-mentioned factors in postnatal life, prenatal intrauterine sensitization to the allergen might be responsible for the development of allergy in their offspring, as allergen-specific T lymphocytes have been reported to be present as early as 22 weeks of gestation.[2]

The present study was undertaken to analyze the possible risk factors for triggering allergy, such as pre- and post-natal maternal symptoms, nutrition, vaccination, and any exposure to animals and tobacco smoke.

Our data showing that the frequency of maternal infections during pregnancy, including diarrhea, fever, rhinorrhea, cough, pharyngitis, bronchitis, and pneumonia strongly correlated with the prevalence of allergy in their offspring, suggest that immunological alterations of the infants could be caused by maternal infections.

Although we have no definite evidence for a link between maternal pharyngitis and atopic dermatitis in their infants, immunological alterations during pregnancy could modify fetal immunity as was reported elsewhere:[9] maternal immunization to dust mites carried out prior to conception inhibited the type I hypersensitivity response of the offspring in an antigen-specific way. Thus, the study and our data suggest that several maternal factors which cause immunological changes during pregnancy also trigger the development of allergy in the offspring. In this scenario, immune cells residing in the mother's pharynx in inflammation were activated by epithelial cells which highly expressed thymic stromal lymphopoietin (TSLP),[10] and subsequently secreted cytokines and mediators. These, in turn, stimulated fetal lymphocytes and enabled these to migrate to the skin of the children. In fact, skin-homing chemokines (ligands) and their receptors include CCL17/TARC (thymus- and activation-regulated chemokine) and CCL22/MDC (monocyte-derived chemokine) and their receptor CCR4, CCL27/CTAC (chemotactic responsiveness to cutaneous T-cell-attracting chemokine) and its receptor CCR10, and E-selectin and its receptor cutaneous lymphocyte-associated antigen (CLA),[11] either of which may be affected by the cytokines and mediators released from the mother's pharynx.

A link between the family history of allergy and the development of allergy in the progeny reflects the active role of both genetic and environmental factors, as reported elsewhere.

In our study, infantile infections were not associated with the development of allergy. Our investigation should, however, be extended to cover the use of antibiotics, because they may increase the incidence of allergic diseases as reported previously.[12]

The present study did not find any link between the feeding of the infants and the development of allergy. Conflicting results have been obtained with regard to the influence of breast-feeding on infantile allergy: breast-feeding may lower the incidence of allergy in children,[13] whereas it may also be a risk factor for the development of allergy.[14] Extensive study in the near future should define the role of breast-feeding on allergic childhood diseases.

In the context of immune dysregulation and allergy, several vaccinations have been linked to the development of allergic diseases in infancy. Particu-

larly noteworthy is the influence of BCG and DPT: BCG has reportedly attenuated the incidence of allergy,[15,16] while the DPT vaccination may promote atopic disorders.[16] The results regarding BCG and DPT in our study disagreed with that. This discrepancy may have resulted from the difference in ages of the individuals studied.

Neither exposure to pet nor environmental tobacco smoke was identified as a risk factor for the development of allergy in this study. The results of the present investigation differ from those showing a positive link between exposure to cats and environmental smoke and childhood allergy.[7] Our study includes only children aged under two years old, inevitably excluding those who would otherwise develop allergic diseases after this age.

In combination, the pre- and post-natal factors that may affect the immune system of the fetus and infants were clearly shown to promote or inhibit the development of allergy respectively. We hope the avoidance of the aforementioned risk factors may prevent the development of childhood allergy.

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