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Timing of eczema onset and risk of food allergy at 3 years of age: A hospital-based prospective birth cohort study

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ABSTRACT

Background: Although recent studies suggest that eczema in early childhood is important in the development of food allergy, the importance of the timing of eczema onset has not been fully clarified.
Objective: This study aim to identify an association between the timing of eczema onset and development of food allergy in a prospective birth cohort study.
Methods: Data were obtained from the Tokyo Children's Health, Illness and Development (T-CHILD) study, which is a hospital-based birth cohort study currently in progress in Japan. A total of 1550 children were born to the recruited women. Outcome data for children were collected from questionnaires completed at 6 months, 1 and 3 years of age. Association between the timing of eczema onset and development of food allergy was estimated by logistic regression analyses. All analysis were performed using SPSS software with a two-sided 5% significance level.
Results: Eczema in the first year of life was a significant risk factor in multivariate analysis (aOR 3.90, 95% CI 2.34–6.52, $p < 0.001$). In each age (by month) stratum, infants with onset of eczema within the first 1–2 months after birth had the highest risk of food allergy at 3 years of age (aOR 6.61, 95% CI 3.27–13.34, $p < 0.001$).
Conclusion: Infants with early eczema onset (especially within the first 1–4 months after birth) were found to have an increased risk of developing food allergy at 3 years of age. Our findings may contribute to a better understanding of the timing of eczema onset as a potentially modifiable risk factor and to defining those who may need to be on guard for food allergy.

1. Introduction

Food allergy, an abnormal immunologic response to causal foods, most often begins early in life and has potential risks of severe reactions such as anaphylaxis [1,2]. The prevalence of food allergy has been increasing worldwide in recent decades, and the estimated prevalence was reported as 10% in infants and 5% in preschool children [3,4]. The burden of food allergy in young children is a serious health issue, substantially affecting the quality of life. Although interplay of genetic and environmental factors generally plays an important role in development of food allergy, environmental exposure is likely the primary cause of the rapid increase in food allergy during the last decade.

Eczema is the most prevalent chronic non-communicable skin disease, affecting up to 30% of children [5,6]. The relationship between eczema and food allergy has been enigmatic, with some controversy regarding which came first, eczema or food allergy [7]. Notably, recent studies in this field have been fruitful, resulting in a paradigm shift in our understanding of allergen sensitization, namely, the dual-allergen exposure hypothesis: oral intake of food proteins tends to induce tolerance, whereas epicutaneous exposure to food proteins tends to induce allergic sensitization [8].

Current evidence suggests that epicutaneous exposure to food proteins via eczema in early childhood is a significant risk factor in the development of food allergy. Since studies to date have been based primarily on case-control and cross-sectional study data

Abbreviations: T-CHILD, Tokyo Children's Health, Illness and Development; OR, odds ratio; CI, confidence interval; ISAAC, International Studies of Asthma and Allergies in Childhood.

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[9,10], it is difficult to exclude alternative explanations such as reverse causation and recall bias. Understanding the timing of eczema onset is of particular interest because eczema may be a modifiable risk factor for food allergy, but prospective birth cohort studies investigating this issue are lacking [11]. Therefore, we investigated the association between the timing of eczema onset and the development of food allergy in a prospective birth cohort study, The Tokyo Children's Health, Illness and Development (T-CHILD) study.

2. Materials and methods

2.1. Study design and population

The T-CHILD study, also known as the "Seiiku Cohort Study", was a single-center, prospective birth cohort study, conducted in the National Center for Child Health and Development (NCCHD), Tokyo, Japan [12,13]. Its objective was to investigate the relationship between exposure variables and the development of allergic diseases and the other disorders prospectively. All pregnant women who visited NCCHD before the 16th week of gestation were consecutively invited to join the T-CHILD study between October 2003 and December 2005. Consequently, 1701 women were enrolled in the T-CHILD study during their first trimester. A total of 1550 children were born to the enrolled women from March 2004 to August 2006.

2.2. Questionnaire

After written informed consent was obtained, the pregnant women were followed using mailed questionnaires. Baseline data were collected from questionnaires completed at 16, 23 and 34 weeks' gestation and their medical charts. Outcome data for children were collected from questionnaires completed at 6 months, 1 and 3 years of age.

2.3. Definitions

Food allergy: Children's food allergy was determined at 1 and 3 years of age by having the parents respond to the question: "Has your child experienced any allergic symptom immediately after food intake as follows: urticaria, swelling, wheezing, cough, vomiting, fainting or becoming unconscious?"

Eczema and wheeze: Children's eczema and wheeze were examined using the International Studies of Asthma and Allergies in Childhood (ISAAC) questionnaire [14,15], which was translated into Japanese and validated through the process of back translation in cooperation with the steering committee members. Presence of eczema was determined using a positive answer to the two ISAAC questions: "Has your child had an itchy rash?" and "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?" The months of age at eczema onset was determined from questionnaires completed at 6 and 12 months of age and classified into five groups based on the timing of eczema onset: 1) less than 1 month, 2) 1–2 months, 3) 3–4 months, 4) 5–8 months and 5) 9–12 months. Presence or absence of wheeze was also determined using a question from ISAAC: "Has your child ever had wheezing or whistling in the chest at any time in the past?"

2.4. Data analysis

In this analysis, if a pregnancy was multiple, we randomly selected and followed only one child from the multiple births. The following factors, known to be associated with food allergy and/or eczema, were considered as potential confounders: gender, birth weight, mode of delivery, season of birth, parental history of allergic diseases, breast feeding, timing of solid food introduction, history of wheeze at 1 year, pet ownership, annual household income, and mother's educational level.

2.5. Statistical analysis

We analyzed for association between eczema until 12 months of age and subsequent food allergy in children who had not experienced food allergy symptoms during their first 12 months. The risk of development of food allergy was also calculated by age at eczema onset. We estimated crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for associations between each variable and food allergy. Logistic regression models were constructed, and the potential confounders described above were included in multivariate models to obtain the adjusted ORs. We also conducted logistic regression analysis of the multiply-imputed data. All tests were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA) with a two-sided 5% significance level.

2.6. Ethical approval

This study was approved by the Ethics Committee of the National Center for Child Health and Development (Acceptance Number #52).

3. Results

3.1. Characteristics and causative foods

Fig. 1 shows the flowchart of the study population in the T-CHILD study. We obtained data for 1504 children. The

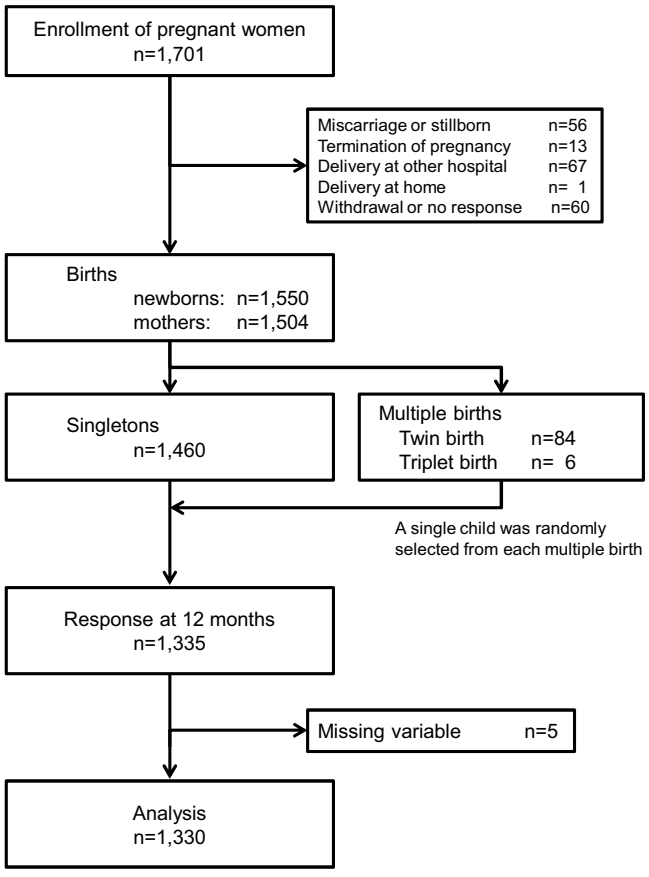

Fig. 1. Flow chart of study population in T-CHILD study.