Original Article

The Association of the Delayed Introduction of Cow's Milk with IgE-Mediated Cow's Milk Allergies

Yutaro Onizawa, MD[a], Emiko Noguchi, MD, PhD[b], Masafumi Okada, MD, PhD[c], Ryo Sumazaki, MD, PhD[d], and Daisuke Hayashi, MD[a] *Ibaraki, Japan*

What is already known about this topic? A few studies have suggested that the early introduction of cow's milk formula might be protective against IgE-mediated cow's milk allergies. However, these studies have limited data about the factors affecting parental choices regarding feeding patterns.

What does this article add to our knowledge? In this case-control study, the delayed introduction of cow's milk formula was an independent risk factor for an IgE-mediated cow's milk allergy. Most parents chose exclusive or almost exclusive breastfeeding because of reasons other than allergy prevention.

How does this study impact current management guidelines? In contrast to the current guidelines, our result suggests that regular consumption of cow's milk formula might play an important role in preventing IgE-mediated cow's milk allergies.

BACKGROUND: Although exclusive breastfeeding at least 4 to 6 months has been recommended to prevent IgE-mediated cow's milk allergy (IgE-CMA), early introduction of food allergens has received a lot of attention in recent years for the prevention of food allergies.

OBJECTIVES: We aimed to determine whether IgE-CMA is associated with a feeding pattern in early infancy.

METHODS: In a case-control study, we retrospectively compared the patient background, past history of atopic dermatitis, bronchial asthma, family history of allergic diseases, feeding patterns in early infancy, and the reason for choosing early infancy feeding patterns of patients with IgE-CMA with age- and sex-matched healthy controls using a questionnaire completed by their mothers. To minimize the influence of confounders, we also compared patients with IgE-CMA with those with IgE-mediated egg allergy (IgE-EA).

RESULTS: A total of 51 patients with IgE-CMA were compared with 102 controls (1:2 matching) and 32 unmatched patients with IgE-EA. In a multivariable logistic regression analysis, the adjusted odds ratio of delayed (started more than 1 month after birth) or no regular cow's milk formula (less than once daily) was 23.74 (95% CI, 5.39-104.52) comparing the CMA group with the Control group, and 10.16 (95% CI, 2.48-41.64) comparing the CMA group with the EA group. Only 3 (6.5%), 2 (4.8%), and 3 (14.3%) mothers in the CMA group, the Control group, and the EA group chose "To prevent allergic disease" as a reason for choosing exclusive or almost exclusive breastfeeding in the first month of life, respectively.

CONCLUSIONS: The early introduction of cow's milk formula is associated with lower incidence of IgE-CMA. © **2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:481-8)**

Key words: *Food allergy; IgE-mediated cow's milk allergy; Breast milk; Allergy prevention*

Cow's milk allergy (CMA) is the second most common food allergy in the United States[1] and Japan[2] and can be potentially fatal.[3] CMA was shown to affect between 0.5% and 4.9% of children, although the prevalence varies because of different diagnostic criteria, study designs, methodologies, and the ethnic background of participants.[4-9] Among CMA-affected children, 48% to 73% are considered to have IgE-mediated CMA (IgE-CMA).[4,9,10] The outgrowth rate of IgE-CMA also differs among studies. Earlier studies have demonstrated good prognoses in patients with CMA. The resolution rate of CMA was reported to be 78% at 6 years of age in a study by Bishop et al in 1984,[11] 92% at 5 years of age in a study by Host et al in 1985,[4] and 85% at 8 years of age in a study by Saarinen et al in 1994.[10] However, studies from the 2000s presented worse prognoses. A large study including 807 subjects by Skripak et al[12] reported a resolution rate of 19% at 4 years of age and 42% at 8 years of age from 1994 to 2007. Likewise, other studies demonstrated a poor prognosis, including a 53% resolution rate at 5 years of age in a

[a]Department of Pediatrics, Ryugasaki Saiseikai Hospital, Ibaraki, Japan
[b]Department of Medical Genetics, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan
[c]Department of Epidemiology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan
[d]Department of Child Health, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan
This study was supported by Management Expenses Grants of University of Tsukuba.
Conflicts of interest: The authors declare that they have no relevant conflicts.
Received for publication July 17, 2015; revised December 29, 2015; accepted for publication January 21, 2016.
Corresponding author: Emiko Noguchi, MD, PhD, Department of Medical Genetics, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan. E-mail: enoguchi@md.tsukuba.ac.jp.
2213-2198

http://dx.doi.org/10.1016/j.jaip.2016.01.012

Abbreviations used
AD- Atopic dermatitis
AAP- American Academy of Pediatrics
ATS-DLD- American Thoracic Society-Division of Lung Diseases
BA- Bronchial asthma
CM- Cow's milk
CMA- Cow's milk allergy
EA- Egg allergy
IgE-CMA- IgE-mediated cow's milk allergy
IgE-EA- IgE-mediated egg allergy
ISAAC- International Study of Asthma and Allergies in Childhood
OR- Odds ratio

study by Wood et al[13] in 2009 and 57% at 5 years of age in a study by Elizur et al[14] in 2004-2006.

To prevent food allergies and IgE-CMA in early childhood, exclusive breastfeeding for at least 4 to 6 months was first recommended by the Section of Paediatrics of the European Academy of Allergology and Clinical Immunology and the American Academy of Pediatrics (AAP) in the early 2000s.[15,16] The delayed introduction of potentially allergenic foods in high-risk infants (eg, dairy products delayed until 1 year; eggs until 2 years; and peanuts, nuts, and fish until 3 years of age) was also recommended by the AAP in 2000. In 2008, the AAP issued a new guideline that there is no current convincing evidence that delaying the introduction of these foods beyond 4 to 6 months has a significant protective effect on the development of allergic disease, although solid foods should not be introduced before 4 to 6 months of age.[15]

Recently, the early introduction of food allergens has received much attention in the prevention of food allergies. In 2008, Du Toit et al[17] compared the prevalence of peanut allergies between Jewish school children in the United Kingdom and those in Israel and reported that the prevalence of peanut allergies in the United Kingdom was 10 times higher than that in Israel (1.85% vs 0.17% for the prevalence of peanut allergies, respectively) and that the early consumption of peanuts in the first years of life is common in Israel but not in the United Kingdom. Subsequently, they conducted a randomized, controlled, open-label trial to determine whether the early introduction of dietary peanuts could serve as an effective strategy for the prevention of peanut allergies and found that the avoidance of peanuts in early infancy was associated with the development of peanut allergies (13.7% in the avoidance group vs 1.9% in the consumption group for the prevalence of peanut allergies, respectively).[18] In addition to peanuts, the early introduction of eggs,[19] cereal grains,[20] and fish[21] was also associated with lower rates of food allergies in a cross-sectional study and a birth cohort study.

Previous studies have suggested the efficacy of the early introduction of cow's milk (CM) to prevent IgE-CMA. In a large birth cohort study of 13,019 infants, Katz et al[9] reported that only 0.05% of the infants who started on regular CM formula within the first 14 days developed IgE-CMA, whereas 1.75% of the infants who started formula between the ages of 105 and 194 days developed IgE-CMA. The other birth cohort study of 6209 infants showed that breastfeeding during the first 2 months at home, whether exclusively or combined with infrequent exposure to small amounts of CM formula, was an independent risk factor for IgE-CMA.[22] CM can be introduced soon after birth in some babies because most infant formula is made with CM, although other foods, such as eggs and peanuts, are, in most cases, introduced after the baby starts solid food at 4 to 6 months of age. Therefore, the factors that affect the feeding patterns of CM formula can be modifiable risk and/or protective factors for developing a milk allergy. The aim of this study was to clarify whether the early introduction of CM formula was associated with IgE-CMA in Japan and to elucidate factors affecting the timing of the introduction of CM formula to babies.

METHODS

Study design and population

This research and study protocol was approved by the ethical committee of Ryugasaki Saiseikai Hospital and the University of Tsukuba Hospital. The patients and controls were recruited at Ryugasaki Saiseikai Hospital from November 2014 to February 2015. Information regarding past histories of allergic diseases, family histories of allergic diseases, and feeding patterns in early infancy was retrospectively collected using a questionnaire after parents gave informed consent to participate in the study.

The CMA group included patients with IgE-CMA who visited Ryugasaki Saiseikai Hospital between October 2013 and February 2015. IgE-CMA was defined as having immediate-type allergic reactions within 2 hours after dairy intake (eg, urticaria, wheezing, vomiting, and diarrhea), positive CM-specific IgE ($\geq$0.7 kUA/L), and a diagnosis by a board-certified allergy specialist (D.H.). The Control group consisted of age- and sex-matched children with 1:2 matching who visited the hospital between November 2014 and February 2015 for a common cold or routine immunization. The inclusion criterion of control subjects was not having a history of CMA or other food allergies (Control). We also recruited patients with egg allergy (EA group) with IgE-mediated egg allergies (IgE-EA) without a history of milk-related food allergies who visited the hospital in the same time periods. IgE-EA was defined as having both immediate-type allergic reaction, positive egg-specific IgE ($\geq$0.7 kU/L), and a diagnosis by the specialist (D.H.). Children were excluded from the study if they (i) were younger than 1 year old at the enrollment, (ii) were a preterm birth (gestational age $<$ 36 weeks), (iii) were of low birth weight ($<$2500 g), (iv) had congenital anomalies, or (v) had non-IgE-CMA.

The questionnaires were completed by parents at the hospital visit. Seven patients in the CMA group who had no appointment between November 2014 and February 2015 completed the questionnaires by a telephone interview administered by the pediatrician (Y.O.).

Feeding patterns

The questionnaire included the following information about feeding patterns in early infancy.

1. Any use of CM formula at the maternity hospital.
2. The timing of the introduction of nonregular CM formula.
3. The timing of the introduction of regular CM formula.
4. Feeding patterns in the first month of life and the reason for choosing these patterns.
5. The timing of discontinuation of CM formula and the reason for discontinuation.

Regular CM formula was defined as the consumption of CM formula at least once daily (regardless of the amount). Early regular continuous CM formula was defined as regular consumption of CM