

Predictors of Persistent Milk Allergy in Children: A Retrospective Cohort Study

Yumi Koike^{a, b} Sakura Sato^a Noriyuki Yanagida^c Tomoyuki Asaumi^c
Kiyotake Ogura^c Kiyotaka Ohtani^{a, d} Takanori Imai^e Motohiro Ebisawa^a

^aClinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, Kanagawa, Japan;

^bDepartment of General Pediatrics, Nagano Children's Hospital, Nagano, Japan; ^cDepartment of Pediatrics, Sagamihara National Hospital, Kanagawa, Japan; ^dDepartment of Pediatrics, Sagamihara Kyodo Hospital, Kanagawa, Japan; ^eDepartment of Pediatrics, Showa University School of Medicine, Tokyo, Japan

Keywords

Cow's milk · Food hypersensitivity · Immunoglobulin E · Oral food challenge · Tolerance acquisition

Abstract

Background: Cow's milk (CM) allergy is the second most common food allergy developed during infancy in Japan. To identify predictors of persistent CM allergy, we investigated the tolerance acquisition rate based on an oral food challenge in children under 6 years of age, diagnosed with immediate-type CM allergy. **Methods:** This retrospective cohort study included 131 children born in 2005 with a history of immediate allergic reaction to CM, of whom 39 were excluded because of ongoing oral immunotherapy ($n = 18$) or a lack of follow-up data ($n = 21$). The 92 remaining participants were followed for 6 years. Tolerance was defined as no adverse reaction to 200 mL of CM and regular intake of milk at home. Subjects were divided into 3 groups based on age at tolerance acquisition: group I (<3 years; $n = 31$), group II (3–6 years; $n = 42$), and group III (persistent allergic group; $n = 19$). **Results:** Tolerance acquisition rates by 3, 5, and 6 years of age were 32.6% (30/92), 64.1% (59/92), and 84.8% (70/92), respectively. Age at first hospital visit was significantly higher

in groups II and III than in group I ($p < 0.001$). The incidence of anaphylaxis to other foods was also higher in group III than in group I ($p = 0.04$), as was CM-induced anaphylaxis ($p = 0.03$). Furthermore, milk and casein-specific immunoglobulin E (IgE) levels were significantly higher in group III than in group II after birth and remained high thereafter ($p < 0.05$). **Conclusions:** The history of anaphylaxis and high milk-specific IgE levels were associated with persistent CM allergy.

© 2018 S. Karger AG, Basel

Cow's milk (CM) allergy is the most widespread food allergy among young children, with a 2–3% global prevalence [1–4], although the rates vary geographically. In Japan, CM allergy is the second most common food allergy in young children [5]. Although there are several reports concerning the natural history of CM allergy from the USA and European countries [1–4, 6–9], few studies have examined it in Asian countries, and only 2 studies have examined the natural history of food allergies in Japan [10, 11]. However, the tolerance acquisition rates based

Edited by: A.W. Burks, Chapel Hill, NC, USA.

on oral food challenge (OFC) and predictors of persistent food allergy in Japanese children up to 6 years of age have not been explored thus far. OFC is a routine diagnostic procedure for diagnosing food allergy and is widely performed in Japan [12].

The aim of this study was to identify the predictors of persistent CM allergy and to investigate the tolerance acquisition rate based on OFC in children under 6 years of age, diagnosed with immediate-type CM allergy. Our retrospective cohort study evaluated clinical records from 131 children born in 2005, who were allergic to CM and had been treated at the Department of Pediatrics, Sagami-hara National Hospital (Kanagawa, Japan). They were followed until 6 years of age. All subjects had a history of immediate allergic reaction to CM, characterized by acute urticaria, angioedema, difficulty in breathing, wheezing, throat tightness, and/or vomiting. Subjects with high milk-specific immunoglobulin E (IgE) levels but a negative OFC result, those who did not consume CM based only on high milk-specific IgE levels, those undergoing CM oral immunotherapy, and those with an incomplete medical history for the observation period were excluded from the study.

Tolerance to CM was determined based on the OFC results. In the present study, participants were subjected to OFC if more than 1 year had lapsed since the last immediate allergic response to CM, to confirm tolerance or when requested by patients or guardians, provided that serum analysis showed reduced CM-specific IgE levels. Subjects tolerant to CM were defined as those who ingested 200 mL of milk without symptoms several times after negative results of OFC. Patients who tolerated 25 mL of milk or 48 g of yogurt during the OFC gradually increased their intake at home, and if they were able to ingest 200 mL of milk, they were considered tolerant. The following factors were analyzed for their association with age at tolerance acquisition: patient background (gestational age; birth weight; type of delivery; sex; method of nutrition during infancy; age at weaning; pet ownership; passive smoking; number of siblings; age at first visit to our hospital; complication rates of bronchial asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis before 3 years of age), family history of allergic complications (including bronchial asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis), and other food allergy factors (age at onset, age at food allergen elimination, and any other history of food-induced anaphylaxis).

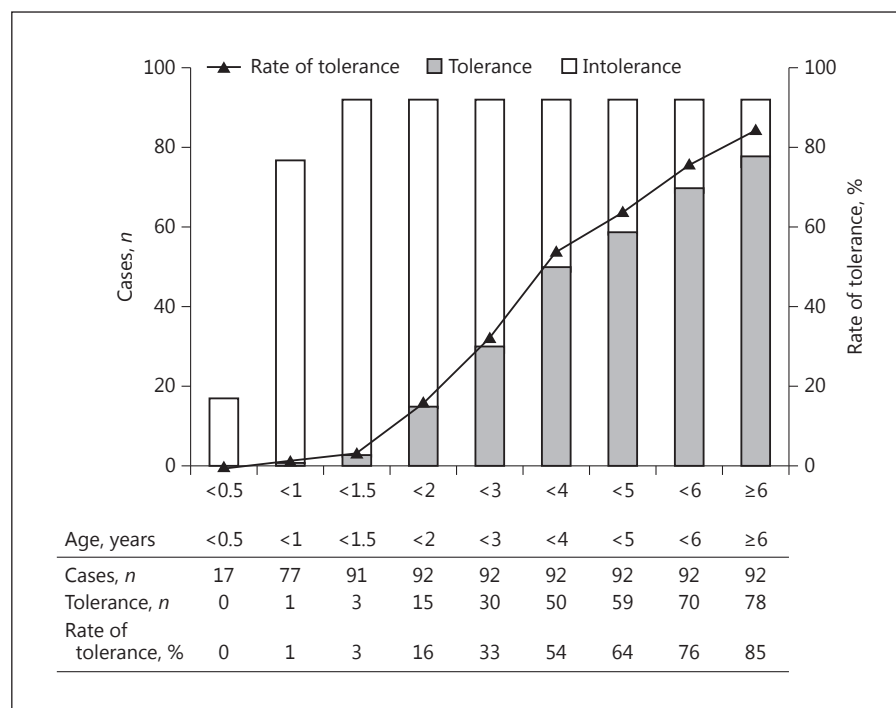
In total, 131 children with a history of immediate-type allergic reaction following CM ingestion visited our de-

partment. Among them, 39 subjects were excluded based on ongoing oral immunotherapy ($n = 18$) or a lack of follow-up data ($n = 21$). The remaining 92 participants were followed for 6 years. Tolerance was defined as no allergic reaction against 200 mL of CM and regular intake of milk at home. Subjects were divided into 3 groups based on age at tolerance acquisition: group I (<3 years; $n = 31$), group II (3–6 years; $n = 42$), and group III (persistent allergic group; $n = 19$) (online suppl. Fig. 1; see www.karger.com/doi/10.1159/000486311 for all online suppl. material).

The correlation between subject age and tolerance to 200 mL of CM is shown in Figure 1. Tolerance acquisition rates at 3, 5, and 6 years were 32.6% (30/92), 64.1% (59/92), and 84.8% (70/92), respectively. The age at the first visit to our hospital was significantly higher in groups II and III compared to group I ($p < 0.001$). The total number of CM-induced anaphylactic events was significantly higher in group III than in group I ($p = 0.03$). It was also significantly higher than the number of food-induced anaphylactic events ($p = 0.04$) (online suppl. Table 1). No significant differences were noted among the 3 groups with regard to details other than the clinical information cited above (online suppl. Table 1). Milk- and casein-specific IgE levels in group III remained significantly higher than those in group I ($p < 0.05$). Specifically, IgE levels remained low in group I throughout the observation period, and the highest levels were observed among group II subjects at 6–12 months of age, which remained elevated thereafter. In contrast, specific IgE levels gradually increased during the study period in group III (online suppl. Fig. 2).

In the present study, based on the OFC results, approximately 80% of children with immediate-type CM allergy could acquire tolerance until 6 years of age. A history of anaphylaxis and high milk-specific IgE levels were associated with persistent CM allergy at 6 years of age. Several reports on the natural history of food allergy have been published from the USA and European countries [1–4, 6–9]. Although the reported rates of CM allergy resolution vary by region and study design [3], a pan-European birth cohort study of 12,049 children in 9 countries by Schoemaker et al. [1] found a CM allergy rate of 0.59%, as confirmed by OFC. Of those with IgE-mediated CM allergy, 57% developed tolerance within 1 year of diagnosis [1]. It is possible that the observed tolerance acquisition rate in our study was lower than those of these cohort studies because all the subjects of our study were from a single study site. Since our institution is a specialty hospital for allergy, patients with severe

Fig. 1. Age-dependent rate of tolerance acquisition for 200 mL of cow's milk (CM). White and shaded bars represent intolerant (persistent CM allergy) and tolerant patients, respectively.



conditions tend to visit the tertiary hospital only after becoming older because they visit the primary hospital during the initial stages. Therefore, the severity of CM allergy in our study might differ from that of the general population.

Meanwhile, it is possible that some of the subjects in this study ingested small amounts of milk before undergoing the OFC, which could affect the rate of tolerance [13]. In this study, we did not account for subjects consuming milk products before OFC. Moreover, subjects received nutritional guidance after an OFC with 25 mL milk and consumed higher amounts of milk, which makes it possible to improve the tolerance rate of milk allergy. Although some of the children allergic to CM had reactions after ingestion of a certain amount of CM, some could consume very low doses of CM without undergoing any allergic reaction [13].

With respect to patient background and other food allergy factors, Skripak et al. [7] specified that complications of bronchial asthma, atopic dermatitis, and high milk-specific IgE levels negatively affected tolerance acquisition, whereas milk-specific IgE levels, milk skin prick test wheal size, and atopic dermatitis severity at diagnosis were the strongest predictors of CM allergy resolution in a separate US study [6]. An earlier study by our department suggested that complications related to vari-

ous food allergies, a history of anaphylaxis, other allergic diseases (atopic dermatitis), and high antigen-specific IgE levels were most predictive of resolution [11]. Similarly, the present study indicated that a history of anaphylaxis triggered by any food ($p = 0.03$) or specifically CM ($p = 0.04$) was significantly more frequent in group III than in groups I and II.

Wood et al. [6] reported that the milk IgE level was an important predictor of the resolution of milk allergy. In our study, milk-specific IgE levels of groups II and III at 6 months of age were significantly higher than that of group I. It was not possible to investigate differences in casein-specific IgE levels because of the small number of subjects who underwent blood sampling at 6 months; however, significant differences were observed from the age of 1 year, similar to the trends seen for milk-specific IgE levels. These findings suggest that increased milk-specific IgE levels may also be a predictive factor for persistent CM allergy.

Several limitations of our study should also be considered when reviewing the data. First, most notably, this was a retrospective study using medical records, and the timing of the OFC might not exactly be defined by age. Second, the participants did not undergo double-blind, placebo-controlled food challenges, which are gold standards for food allergy diagnosis. Third, patients with mild

CM allergy did not visit our specialty hospital, because they visited the primary hospital.

In conclusion, this analysis, based on the results of OFC, revealed that a history of anaphylaxis and high milk-specific IgE levels were risk factors involved in persistent CM allergy.

Acknowledgment

The authors thank Dr. Akinori Syukuya from Futaba Kodomo Clinic and our coworkers at Sagamihara National Hospital. This study was funded by Health and Labor Sciences Research Grants

for Allergic Disease and Immunology from the Ministry of Health, Labor, and Welfare of Japan. We would like to thank Editage (www.editage.com) for English language editing and publication support.

Disclosure Statement

M. Ebisawa received research support from Health and Labor Sciences Research Grants for Research on Allergic Diseases and Immunology from the Ministry of Health, Labor, and Welfare, Japan (201414009A). M. Ebisawa is on the DBV Technologies Scientific Advisory Board. M. Ebisawa received lecture fees from Pfizer and Siemens. The rest of the authors declare that they have no relevant conflicts of interest.

References

- 1 Schoemaker AA, Sprickelman AB, Grimshaw KE, Roberts G, Grabenhenrich L, Rosenfeld L, Siegert S, Dubakiene R, Rudzvieciene O, Reche M, Fiandor A, Papadopoulos NG, Malamitsi-Puchner A, Fiocchi A, Dahdah L, Sigurdardottir ST, Clausen M, Stańczyk-Przyłuska A, Zeman K, Mills EN, McBride D, Keil T, Beyer K: Incidence and natural history of challenge-proven cow's milk allergy in European children – EuroPrevall birth cohort. *Allergy* 2015;70:963–972.
- 2 Warren CM, Jhaveri S, Warrier MR, Smith B, Gupta RS: The epidemiology of milk allergy in US children. *Ann Allergy Asthma Immunol* 2013;110:370–374.
- 3 Schrandt JJ, van den Bogart JP, Forget PP, Schrandt-Stumpel CT, Kuijten RH, Kester AD: Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. *Eur J Pediatr* 1993;152:640–644.
- 4 Jassica S, Scott S, Robert W: The natural history of food allergy. *J Allergy Clin Immunol* 2016;4:196–203.
- 5 Ebisawa M, Ito K, Fujisawa T; Committee for Japanese Pediatric Guideline for Food Allergy; Japanese Society of Pediatric Allergy and Clinical Immunology; Japanese Society of Allergology: Japanese guidelines for food allergy 2017. *Allergol Int* 2017;66:248–264.
- 6 Wood RA, Sicherer SH, Vickery BP, Jones SM, Liu AH, Fleischer MD, Henning AK, Mayer L, Burks AW, Grishin A, Stablein D, Sampson HA: The natural history of milk allergy in an observational cohort. *J Allergy Clin Immunol* 2013;131:805–812.
- 7 Skripak JM, Matsui EC, Mudd K, Wood RA: The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2007;120:1172–1177.
- 8 Elizur A, Rajuan N, Goldberg MR, Leshno M, Cohen A, Katz Y: Natural course and risk factors for persistence of IgE-mediated cow's milk allergy. *J Pediatr* 2012;161:482–487.
- 9 Saarinen KM, Pelkonen AS, Makela MJ, Savilahti E: Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol* 2005;116:869–875.
- 10 Ikematsu K, Tachimoto H, Sugisaki C, Syukuya A, Ebisawa M: Feature of food allergy developed during infancy. 2. Acquisition of tolerance against hen's egg, cow's milk, wheat, and soybean up to 3 years old (in Japanese). *Arerugi* 2006;55:533–541.
- 11 Imai T, Komata T, Ogata M, Tomikawa M, Tachimoto H, Shukuya A, Ebisawa M: Prolonged type of food allergy (in Japanese). *Arerugi* 2007;56:1285–1292.
- 12 Ebisawa M, Nishima S, Ohnisi H, Kondo N: Pediatric allergy and immunology in Japan. *Pediatr Allergy Immunol* 2013;24:704–714.
- 13 Okada Y, Yanagida N, Sato S, Ebisawa M: Better management of cow's milk allergy using a very low dose food challenge test: a retrospective study. *Allergol Int* 2015;64:272–276.

131 CM allergy with immediate type for subjects who were born in 2005

39 subjects excluded

1) 18 subjects who underwent OIT

2) 21 subjects who were not followed-up until 6 years

92 subjects analyzed

Definition of tolerance acquisition:

Negative for OFC response after drinking 200 mL of milk, reconfirmed at home.

Group I
(31 subjects who
outgrew CM allergy
at < 3 years)

Group II
(42 subjects who
outgrew CM allergy
between 3 and 6 years)

Group III
(19 subjects with CM
allergy even at 6 years)

Supplementary figure 1. Flow diagram of the study methodology.

Patients with immediate-type CM allergy born in 2005 were enrolled in the study ($n = 131$).

Among them, 39 subjects were excluded. The remaining 92 subjects were divided into 3

groups based on age at tolerance acquisition as follows: group I ($n = 31$), group II ($n = 42$), and

group III ($n = 19$).

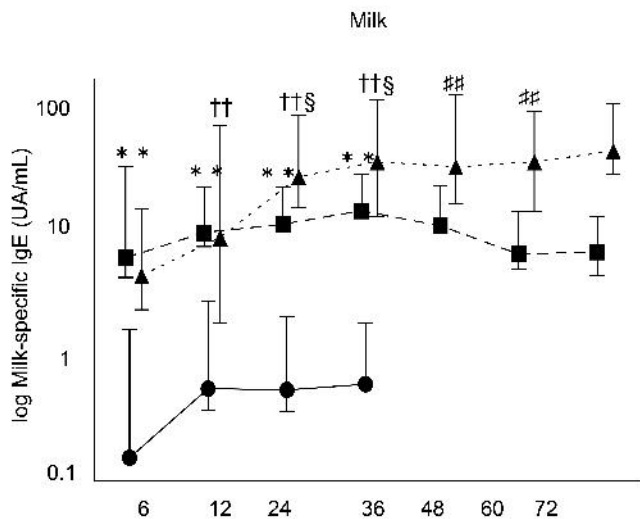
Supplementary figure 2. Association between milk- and casein-specific IgE levels and age.

Participants in groups I, II, and III are represented by circles, squares, and triangles,

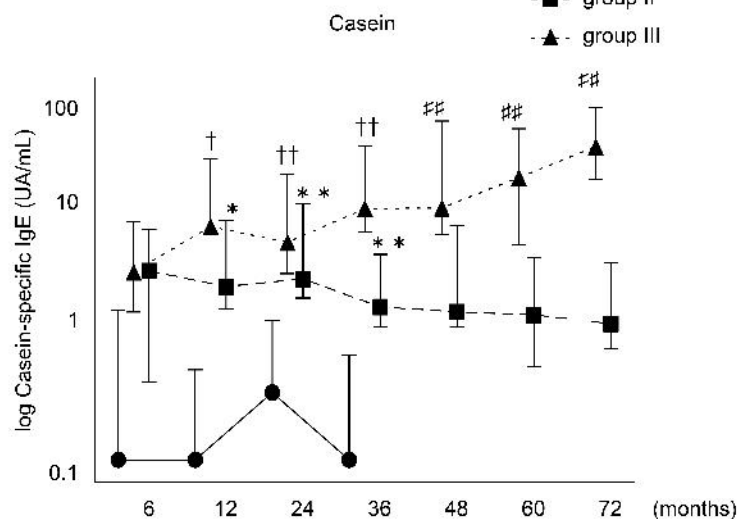
respectively. Milk- and casein-specific IgE levels are shown below each graph. * $p < 0.05$, ** $p <$

0.01 vs. group I, [†] $p < 0.05$, ^{††} $p < 0.01$ vs. group I, [§] $p < 0.05$ vs. group II by the Kruskal–Wallis

test; ^{##} $p < 0.01$ vs. group II by the Mann–Whitney U -test.



Months	6	12	24	36	48	60	72
group I (n = 31)	15	19	18	15			
group II (n = 42)	19	25	30	33	27	15	11
group III (n = 19)	8	10	11	11	12	13	11



Months	6	12	24	36	48	60	72
group I (n = 31)	5	20	18	11			
group II (n = 42)	2	9	8	26	22	12	6
group III (n = 19)	2	8	6	8	12	12	5

Kruskal-Wallis test:

*p ** p<0.01

† p<0.05, †† p<0.01

§ p<0.05 vs. group II

Mann-Whitney test:

p<0.01

vs. group II

Methods

Oral food challenge

Oral food challenge (OFC) procedures were based on the recommended practices of the Japanese Guideline for Food Allergy [7] and the European Academy of Allergy and Clinical Immunology (EAACI) [24]. Briefly, pumpkin cakes containing 25 or 50 mL of CM were cooked at 1000 W for 90 s in a microwave. Almost all subjects underwent an OFC with 25 mL CM, which is a low dose. Meanwhile, patients who were likely to pass the OFC at a base dose of 25 mL because of accidental ingestion of milk were subjected to an OFC of 50 mL. After consumption, participants were monitored for objective symptoms of hypersensitivity on the skin, or respiratory, digestive, circulatory, and nervous symptoms. Patients with objective symptoms who did not require medical treatment were considered negative.

Specific IgE for milk and casein

Serum milk- and casein-specific IgE antibody levels were measured with the ImmunoCAP assay system (Thermo Fisher Scientific/Phadia, Uppsala, Sweden). Specific IgE for milk and casein were examined at 6 months and every 1 year after 1 year of age.

Statistical analysis

Data were analyzed using GraphPad Prism 5 for Windows (GraphPad Software Inc., La Jolla, CA, USA) and presented as the median and interquartile range (IQR). Fisher's exact or Mann–Whitney *U* tests were used for intergroup comparisons of discontinuous variables, whereas Kruskal–Wallis tests were used for comparisons among all 3 groups.

Statistical significance was defined as $p < 0.05$.

Supplementary Table 1. Analyzed factors associated with tolerance acquisition

	Group I (<i>n</i> = 31)	Group II (<i>n</i> = 42)	Group III (<i>n</i> = 19)	<i>p</i> value
Gestational age (wk)				
Median	39.9	39.7	39.3	ns [*]
IQR	38.5–40.7	39.0–40.3	38.3–40.2	
Body weight at birth (g)				
Median	3156.5	3206	3008.0	ns [*]
IQR	2888.0–3324.5	3041.0–3506.0	2780.0–3097.0	
Normal delivery, <i>n</i> (%)	27 (87)	38 (90)	14 (74)	ns [#]
Male, <i>n</i> (%)	17 (55)	22 (52)	11 (42)	ns [#]
Breastfeeding, <i>n</i> (%)	9 (29)	18 (43)	8 (42)	ns [#]
Beginning of weaning (mo)				
Median	5.0	6.0	6.0	ns [*]
IQR	5.0–6.75	6.0–6.8	6.0–6.5	
Pets at home, <i>n</i> (%)	2 (6)	5 (12)	2 (10)	ns [#]
Passive smoking, <i>n</i> (%)	11(35)	9 (21)	7 (36)	ns [#]
Number of siblings (<i>n</i>)				
Median	1.0	2.0	1.0	ns [*]
IQR	1.0–2.0	1.0–2.0	1.0–2.0	
Age at first visit (mo)				
Median	9.2	13.2	48.0	<0.001 [*]
IQR	5.0–13.0	8.4–36.4	15.6–61.2	
Onset of food elimination (mo)				
Median	7.0	6.0	6.0	ns [*]
IQR	5.0–9.0	5.5–7.5	4.0–8.5	
History of An (any foods; times)				
Median	0.0	0.0	1.0	0.04 ^{**}
IQR	0.0–0.0	0.0–0.0	0.0–1.25	
History of An (CM; times)				0.03 ^{**}

	Median	0.0	0.0	1.0	
	IQR	0.0–0.0	0.0–1.0	0.0–1.25	
Allergic factors	BA, <i>n</i> (%)	11 (35)	12 (29)	7 (36)	ns [#]
	AD, <i>n</i> (%)	21 (68)	31 (74)	16 (84)	ns [#]
	AR, <i>n</i> (%)	1 (3)	3 (7)	4 (21)	ns [#]
	AC, <i>n</i> (%)	1 (3)	1 (2)	2(10)	ns [#]

p-values were calculated by the ^{*}Kruskal–Wallis test (^{**} vs. group I) or [#]Fisher’s exact test.

mo: months, ns: not significant, g: grams, CM: cow’s milk, FA/AD: infant atopic dermatitis-associated food allergy, An: anaphylaxis, BA: bronchial asthma, AD: atopic dermatitis, AR: allergic rhinitis, AC: allergic conjunctivitis