Asia Pacific allergy

pISSN 2233-8276 · eISSN 2233-8268

Original Article

http://dx.doi.org/10.5415/apallergy.2013.3.3.179
Asia Pac Allergy 2013;3:179-185

Sensitization patterns of cow's milk and major components in young children with atopic dermatitis

Jeong-Min Lee, Jong-Seo Yoon, Se-Ah Jeon, and Soo-Young Lee*

Department of Pediatrics, Ajou University School of Medicine, Suwon 443-749, Korea

Background: Cow's milk (CM) is one of the most common food allergens in children with atopic dermatitis (AD), and the component-specific immunoglobulin E (component-IgE) measurement has recently become available.

Objective: This study aimed to investigate the sensitization patterns to CM and 3 major components and their clinical values in young Korean children with AD.

Methods: Cow's milk-specific IgE (CM-IgE), α-lactalbumin-specific IgE (ALA-IgE), β-lactoglobulin-specific IgE (BLG-IgE), and casein-specific IgE (Cas-IgE) levels from the sera of patients with AD were measured using the UniCAP™ system (Thermo Fisher Scientific, Sweden) and collected from January 2004 to December 2010. Patients ≥ 4 years of age were excluded from the analysis.

Results: A total of 950 patients diagnosed with AD were ultimately enrolled in the study. Among them, 471 (49.6%) patients were sensitized to CM (CM-IgE[+], > 0.35 kU/L). Sensitization to casein (n = 349, 74.1%) was most common, followed by ALA (n = 283, 60.1%), and BLG (n = 245, 52.5%). Meanwhile, 95 patients had at least 2 follow-up tests. Eighty (84.2%) of these patients tested positive to CM, and the casein sensitization rate was the highest (n = 65, 81.3%). In addition, 479 (50.4%) patients were not sensitized to CM (CM-IgE[–], ≤ 0.35 kU/L) but 35 (7.3%) patients were sensitized to at least one component. Among them, a telephone survey was accessible in 21 cases. A total of 8 (38.1%) patients still suffered from adverse reactions after consuming milk and/or dairy foods.

Conclusion: Casein was the most commonly and persistently sensitized component in CM-IgE(+) children with AD. Measuring CM component IgE antibodies, especially Cas-IgE, is helpful for evaluating problematic allergens in young children with AD.

Key words: Atopic dermatitis; Children; Cow's milk; Casein

Correspondence: Soo-Young Lee
Department of Pediatrics, Ajou University School of Medicine, 206 world cup-ro, Yeongtong-gu, Suwon 443-749, Korea
Tel: +82-31-219-5160
Fax: +82-31-219-5169
E-mail: jsjs87@ajou.ac.kr

Received: June 19, 2013
Accepted: July 12, 2013

INTRODUCTION

Food allergies affect up to 6% of children in the first few years of life, and approximately 50% of patients with atopic dermatitis (AD) have at least one food allergy [1, 2]. Cow's milk (CM) is one of the most common causes of food allergy, with 2-3% of children < 3 years of age having allergic reactions to CM [3-5]. Although 70-80% of these affected children outgrow the sensitivity by the age of 3, the other 20-30% do not [4, 5].

Several studies have aimed to identify the correlations between clinical CM allergy and component-specific immunoglobulin E (IgE) antibodies (component-IgE) in children with CM allergy. CM proteins are divided into 2 groups: casein and whey. Casein accounts for approximately 80% of the total protein content in CM, while whey proteins comprise the rest. Newly developed methods have demonstrated that casein consists of 4 protein fractions, αs1-, αs2-, β-, and κ-casein, comprising 32%, 10%, 28%, and 10% of the total CM protein, respectively [6]. The whey fraction contains α-lactalbumin (ALA) and β-lactoglobulin (BLG), which comprise 5% and 10% of the total CM protein, respectively [7].

Studies have indicated that children with higher concentrations of specific IgE antibody to CM (CM-IgE) are predisposed to persistent CM allergy [8, 9]. Further studies have documented that children with persistent CM allergy have elevated levels of casein-specific IgE antibodies (Cas-IgE) compared with children who have transient CM allergy [8, 10]. Hence, Cas-IgE is dominant in older children and adults with CM allergy [11, 12].

In addition, the identification of the epitopes of an allergenic molecule has provided a growing body of evidence that suggests that casein is a major allergenic component that should be measured in the course of managing CM allergy to evaluate whether an individual has clinically or serologically outgrown the allergy. Microarray technology has confirmed that IgE to distinct allergenic components of CM proteins can be used as a marker of persistent allergy [6, 13]. Indeed, αs1-casein was predominantly observed in persistent CM allergy [13, 14].

With these backgrounds, to evaluate the patterns and clinical significance of CM and major CM components in children with AD, we sought to measure the concentrations of IgE to CM and CM components in infants and young children.

MATERIALS AND METHODS

Subjects

From January 2004 to December 2010, 950 patients < 4 years of age visited our outpatient clinic for AD, and to exclude CM allergy, their concentrations of IgE to CM, ALA, BLG, and casein were evaluated. Medical records were reviewed and a telephone survey was used to document each patient's current symptoms upon milk intake. Patients with either a convincing or vague history of CM allergy were included. We considered urticaria, angioedema, and anaphylaxis as convincing histories, while patients who had a history of aggravated AD after the ingestion of dairy foods and/or CM and/or breast milk without having completed a confirmative food challenge test met the definition of vague history. Subjects were divided into 2 age groups (< 2 years of age, 2-4 years of age) and patients who underwent a follow-up test every 6-12 months after milk avoidance were defined as follow-up patients.

Analyses of specific IgE levels to CM, ALA, BLG, and casein

Venous blood samples of all patients were collected at their first visits. The obtained serum probes were stored at -20℃ and further analyses were performed within 5 days. Specific IgE levels to CM (CM-IgE), ALA (ALA-IgE), BLG (BLG-IgE), and casein (Cas-IgE) in the patients' sera were measured and collected using a UniCAP™ system (Thermo Fisher Scientific, Uppsala, Sweden) according to manufacturer's instructions. Levels > 0.35 kU/L were defined as "positive," while patients with positive results were identified as "sensitized" to the allergen(s). The diagnostic decision points (DDP) of CM were then quoted from earlier studies [15, 16]. Patients < 2 years of age with CM-IgE levels ≥ 5 kU/L and patients 2-4 years of age with CM-IgE levels ≥ 15 kU/L were identified as "sensitized to CM at over DDP."

Statistics

Microsoft Excel 2010 was used to calculate the positive rate among the various groups. All statistical tests were 2-sided, and a level of significance < 5% was considered significant. Bonferroni correction was used to compare paired values among subjects. Corrective data were calculated by R version 2.14.1. Spearman's coefficient with SPSS version 17.0 software (SPSS, Chicago, IL, USA) was used to analyze the correlations among the concentrations of CM-, ALA-, BLG-, and Cas-IgE.

http://dx.doi.org/10.5415/apallergy.2013.3.3.179

RESULTS

Subjects

A total of 950 patients were included in this study. All of these children were diagnosed with AD during their first 4 years of life. The diagnosis was confirmed by our investigators according to the criteria of Hanifin and Rajka [17]. A total of 858 (90.3%) patients were < 2 years of age, while 92 (9.7%) patients were 2-4 years of age. The median age was 2 years (range, 1 month to 3 years, 11 months). The subjects were predominantly male (n = 607, 63.9%).

Sensitization rate of specific IgE to CM, ALA, BLG, and casein

A total of 471 (49.6%) patients were sensitized to CM. Regardless of CM-IgE concentration, the sensitization rate to CM was significantly higher in the older age group (412/858, 48.0% vs. 59/92, 64.1%; $p < 0.005$). The most commonly sensitized component in CM-IgE(+) patients was casein, followed by ALA and BLG in all patients and the younger age group, respectively ($p < 0.001$). Among all subjects, Cas-IgE was positive in 74.1% (n = 349), ALA-IgE in 60.1% (n = 283), and BLG-IgE in 52.5% (n = 245). In the younger age group, Cas-IgE was positive in 74.0% (n = 305), ALA-IgE in 60.0% (n = 247), and BLG-IgE in 53.4% (n = 220). In the older age group, the positive rate of Cas-IgE was higher than that of BLG-IgE (44/59, 74.6% vs. 25/59, 42.4%; $p < 0.005$) and ALA-IgE (44/59, 74.6% vs. 36/59, 61.0%; $p = 0.503$) (Table 1).

Moreover, the sensitization rate to casein was highest regardless of the DDP. In the younger age group, 264 (64.1%) patients had a CM-IgE concentration lower than the DDP; of them, Cas-IgE positivity was higher than that for ALA-IgE (62.9% vs. 50.8%; $p = 0.415$) and BLG-IgE (62.9% vs. 39.8%; $p = 1.133$). The prominent sensitization rate to Cas-IgE was even more significant in younger patients with CM-IgE concentrations higher than the DDP. A total of 93.9% (n = 139) of them were sensitized to casein, while the positive rate of ALA-IgE (n = 113) was 76.4% and that of BLG-IgE was 77.7% ($p < 0.001$). In the older age group with CM-IgE concentrations lower than the DDP (n = 51), the sensitization rate to Cas-IgE was higher than that to ALA-IgE (70.6% vs. 54.9%; $p = 0.455$) and BLG-IgE (70.6% vs. 33.3%; $p < 0.005$). In the older age group with a higher CM-IgE concentration than DDP (n = 8), the sensitization rates to all 3 components were 100% (Table 2).

Sensitization rate of specific IgE to CM, ALA, BLG, and casein in follow-up patients

A total of 95 patients had at least 2 follow-up tests after milk avoidance. Among them, 84% (n = 80) were persistently sensitized to CM in their final test. Cas-IgE was more commonly detected than ALA-IgE (81.3% vs. 58.8%; $p = 0.010$) and BLG-IgE (81.3% vs.

Table 1. Sensitization rate of CM-, ALA-, BLG-, and Cas-IgE in children with atopic dermatitis

	Total	< 2 yr	≥ 2 and < 4 yr	*p* value*
CM-IgE† > 0.35 kU/L	471/950 (49.6%)	412/858 (48.0%)	59/92 (64.1%)	<0.005
ALA-IgE‡ > 0.35 kU/L	283/471 (60.1%)	247/412 (60.0%)	36/59 (61.0%)	0.980
BLG-IgE§ > 0.35 kU/L	245/471 (52.5%)	220/412 (53.4%)	25/59 (42.4%)	0.150
Cas-IgE‖ > 0.35 kU/L	349/471 (74.1%)	305/412 (74.0%)	44/59 (74.6%)	1.000

*Comparison of two age groups (Bonferroni correction, Corrective data was calculated by R version 2.14.1), †cow's milk specific IgE, ‡alpha lactalbumin specific IgE, §beta lactoglobulin specific IgE, ‖casein specific IgE.

Table 2. Sensitization rate of ALA-, BLG-, and Cas-IgE according to the diagnostic decision points of cow's milk (CM) by age in infants and young children with atopic dermatitis

CM-IgE*	< 2 yr		≥ 2 and < 4 yr	
	> 0.35kU/L and < 5 kU/L	≥ 5 kU/L	> 0.35 kU/L and < 15 kU/L	≥ 15 kU/L
ALA-IgE† > 0.35 kU/L	134/264 (50.8%)	113/148 (76.4%)	28/51 (54.9%)	8/8 (100%)
BLG-IgE‡ > 0.35 kU/L	105/264 (39.8%)	115/148 (77.7%)	17/51 (33.3%)	8/8 (100%)
Cas-IgE§ > 0.35 kU/L	116/264 (62.9%)	139/148 (93.9%)	36/51 (70.6%)	8/8 (100%)

*cow's milk specific IgE, †alpha lactalbumin specific IgE, ‡beta lactoglobulin specific IgE, §casein specific IgE.

50.0%; $p < 0.001$). In addition, concentrations of CM-IgE in follow-up patients were further evaluated with DDP according to age. In both age groups with CM-IgE concentrations higher than the DDP, Cas-IgE positivity was 100% (26/26, 100% vs. 12/12, 100%) (Table 3).

Clinical symptoms in patients who were CM-IgE-negative but CM component-IgE-positive

Among the 950 total subjects, 479 (50.4%) patients were not sensitized to CM. Of them, 35 (7.3%) were sensitized to ALA, BLG, or casein. A telephone survey was conducted and detailed recent clinical reactivity to CM was collected in 21 cases. Eight (38.1%) patients had adverse reactions upon dairy food intake. Five of them had a definite history of IgE-mediated reactions. One patient who was ALA-IgE(+) and CM-IgE(–) experienced a rash and swelling immediately after milk intake. Two patients who were Cas-IgE(+), one who was ALA-IgE(+), and another who was BLG-IgE(+) and CM-IgE(–) developed rashes upon ingesting large quantities of milk (200-800 mL). The other 3 patients experienced diarrhea 2-4 hours after milk ingestion. Challenge tests were not performed in these patients (Table 4).

Correlation coefficient comparing CM-IgE and CM component-IgE concentrations

To understand the correlation between the CM-IgE and component-IgE concentrations in children with AD, we analyzed the concentrations of CM-, ALA-, BLG-, and Cas-IgE in each subject. There was a strong positive correlation between the concentrations of CM-IgE and Cas-IgE ($r = 0.806$; $p < 0.001$). Further, statistically significant correlations between CM-IgE and ALA-IgE concentrations ($r = 0.494$; $p < 0.001$) and BLG-IgE concentration ($r = 0.613$; $p < 0.001$) were observed (Figs. 1, 2, and 3).

DISCUSSION

Food allergy is a risk factor of the development, persistence, and exacerbation of AD and has been shown to trigger AD in 30-40% of children with moderate to severe AD [18]. Therefore, upon the

Table 3. Sensitization rate of ALA-, BLG-, and Cas-IgE in follow-up patients according to the diagnostic decision points of cow's milk (CM) by age in infants and young children with atopic dermatitis

CM-IgE*	Total	< 2 yr	≥ 2 and < 4 yr
	> 0.35 kU/L	≥ 5 kU/L	≥ 15 kU/L
ALA-IgE† > 0.35 kU/L	47/80 (58.8%)	21/26 (80.1%)	9/12 (75%)
BLG-IgE‡ > 0.35 kU/L	40/80 (50%)	16/26 (61.5%)	9/12 (75%)
Cas-IgE§ > 0.35 kU/L	65/80 (81.3%)	26/26 (100%)	12/12 (100%)

*cow's milk specific IgE, †alpha lactalbumin specific IgE, ‡beta lactoglobulin specific IgE, § casein specific IgE.

Table 4. Recent clinical symptoms in patients who were CM-IgE(–) but CM component-IgE(+)

Patient No.	Sex	Age (months)	CM-IgE*	ALA-IgE†	BLG-IgE‡	Cas-IgE§	CM provoked symptoms
1	M	5	0.30 kU/L	0.40 kU/L	0.30 kU/L	0.30 kU/L	Rash, Swelling
2	M	36	0.35 kU/L	0.35 kU/L	0.35 kU/L	0.36 kU/L	Rash
3	F	14	0.30 kU/L	0.30 kU/L	3.05 kU/L	0.30 kU/L	Rash
4	M	12	0.35 kU/L	1.15 kU/L	0.35 kU/L	0.35 kU/L	Rash
5	M	8	0.30 kU/L	0.30 kU/L	0.30 kU/L	0.38 kU/L	Rash
6	M	6	0.30 kU/L	0.38 kU/L	0.12 kU/L	0.18 kU/L	Diarrhea
7	F	36	0.35 kU/L	0.35 kU/L	0.35 kU/L	1.35 kU/L	Diarrhea
8	F	4	0.35 kU/L	0.81 kU/L	0.35 kU/L	0.35 kU/L	Diarrhea

*cow's milk specific IgE, †alpha lactalbumin specific IgE, ‡beta lactoglobulin specific IgE, §casein specific IgE.

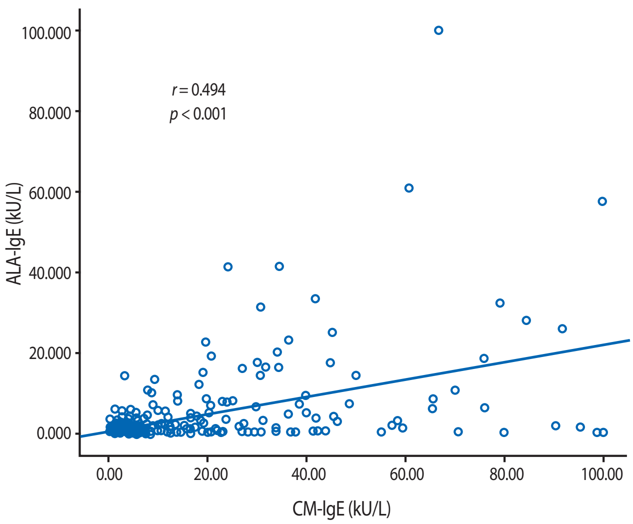

Fig. 1. Correlation between the concentration of CM-IgE and ALA-IgE in infants and young children with atopic dermatitis. There was a statistically significant correlation between the levels of CM-IgE and ALA-IgE ($r = 0.494$; $p < 0.001$). CM-IgE, cow's milk-specific IgE (kU/L); ALA-IgE, α-lactalbumin-specific IgE (kU/L).

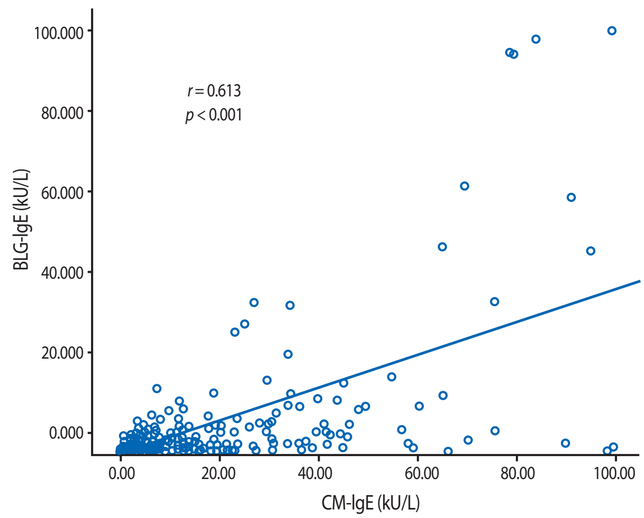

Fig. 2. Correlation between the concentration of CM-IgE and BLG-IgE in children with atopic dermatitis. There was a statistically significant correlation between the level of CM-IgE and ALA-IgE. ($r = 0.613$; $p < 0.001$). CM-IgE, cow's milk-specific IgE (kU/L); BLG-IgE, β-lactoglobulin-specific IgE (kU/L).

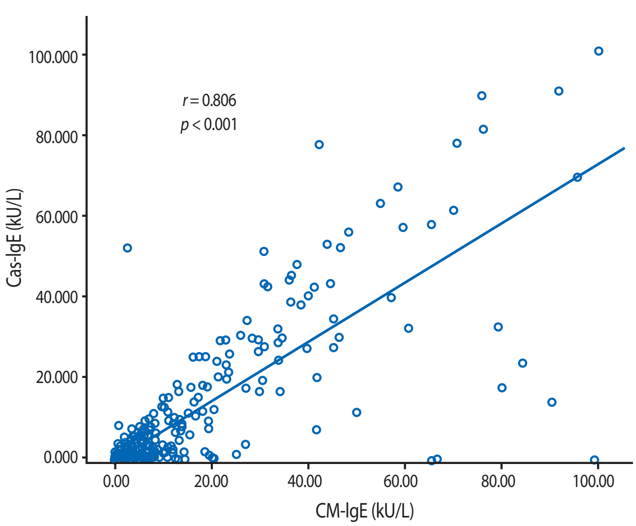

Fig. 3. Correlation between the concentration of CM-IgE and Cas-IgE in children with atopic dermatitis. There was a statistically significant correlation between the level of CM-IgE and Cas-IgE ($r = 0.806$; $p < 0.001$). CM-IgE, cow's milk-specific IgE (kU/L); Cas-IgE, casein-specific IgE (kU/L).

development eczema, young children often visit the pediatrician and receive diagnoses of AD and food allergy. The use of double-blind, placebo-controlled food challenges has revealed that the major symptom-provoking foods include egg, milk, wheat, and soy. Therefore, many clinicians adopt the above food screening test when they assess patients with AD, especially those who develop it at the time they are weaned from breastfeeding [19, 20]. CM is one of the most important food allergens in children; therefore, we evaluated the sensitization rate of CM and its 3 major components in relatively large numbers of patients < 4 years of age with AD. Although we could not perform the challenge test, we aimed to evaluate the sensitization rate to CM as well as each major component and elucidate their correlations to find the persistency markers for CM sensitization.

The UniCAP™ system (Thermo Fisher Scientific) is considered a clinically useful laboratory test because the concentrations of allergen-specific IgE are correlated with blinded food challenges to a few selected foods including CM. Several studies have shown a correlation between the concentration of allergen-specific IgE and the probability of clinical reactivity [15, 16]. Lower IgE levels are associated with earlier resolution of food allergy, and the rate of the decrease of serum IgE levels can be a predictor of when challenges are appropriate [21, 22]. However, without a history of a suspected allergic reaction, a "diagnostic" point alone cannot be used to diagnose a definite food allergy. Furthermore, patients who are not sensitized to (< 0.35 kU/L) certain foods still have a probability of clinical reactions because the antigens in the UniCAP™ system (Thermo Fisher Scientific) do not always include whole problematic food proteins [21, 23].

Cross-reactivity between unpredictable foods remains a possible problem in patients with suspected food allergies [23]. Nevertheless, in vitro measurement is preferred in patients with skin diseases such as AD or urticaria. In addition, numerous studies have suggested that the component is the best discriminator between persistent and transient CM allergy [6, 8, 11]. Severe reactions to CM can be predicted by the high levels of CM-IgE and Cas-IgE in combination with asthma [11, 24]. Moreover, casein was often found to be the cause of reactions in patients with CM allergy who ate so-called non-dairy products that actually used casein as an extender (e.g., sausage, soups, and stews) [11, 25]. However, those previously quoted reports were mostly performed in Western countries. One feature of food allergies is that the prevalence and etiology differ from country to country under the influence of region, food culture, and age [26]. Therefore, this study aimed to analyze the distributions of specific IgE levels to whole CM and CM components in infants and young children in Korea. The median age of the patients in the current study was 2 years, and many of them had no prior exposure to milk.

This study has limitations in that the patients' clinical symptoms were gathered without the use of confirmative challenge tests. Since patients are not clinically confirmed allergic to milk but only sensitized to CM, the severity of clinical reactivity, possibility of regression, and the possibility of tolerance according to the levels of CM-IgE or component-IgE could have not been assessed. However, this study's findings indicated that approximately half of these young patients with AD were sensitized to CM and that, regardless of age or CM-IgE concentration, sensitization to casein is most common among the 3 available components. Sensitization to CM is more significant at older ages, but careful analysis is needed because older patients in this study tended to have rather confident CM allergy histories compared to the infants, who still needed to undergo a food allergen screening test.

Understanding the major problematic allergens in food allergy is still an important issue, especially for infants and young children with AD whose parents need awareness before they wean their children from breastfeeding. After a patient is diagnosed with a food allergy, the general treatment principles at this age include strict avoidance of the food and considering a maternal elimination diet in breastfed infants [27, 28]. In practice, when we assess infant AD for the first time, we face the dilemmas of what to do and how to do it for the diagnosis. Infants are rarely directly exposed to a particular food, so adverse reaction histories to that food are vague. History alone is not enough to select which allergen-specific IgE tests need to be performed. Furthermore, infants are too young for skin prick tests to assess allergen sensitization. Moreover, the use of a radioallergosorbent test alone does not provide sufficient results in some patients, particularly those in this age group whose concentrations of specific IgE to certain foods is often very low [28]. Therefore, to make a food allergy diagnosis in infants, clinicians must first understand the possible allergens in order of priority. This study demonstrated the value of measuring CM-IgE in young children with AD.

Moreover, the results of this study suggest that casein is an important component that should never be omitted from food allergy evaluations in infants. Here we analyzed the data of both infants (< 2 years of age) and young children 2-4 years of age with AD and correlated the findings with the DDP, which has a 95% positive predictive value of clinical reactivity. Casein was revealed as the most commonly sensitized allergen in patients who were CM-IgE(+). In addition, follow-up of patients revealed that sensitization to casein was significant in patients with persistent CM-IgE(+). This result implies that measuring CM component-IgE, especially Cas-IgE with CM-IgE, is critical for assessing CM allergy. Moreover, to predict outgrowth of or tolerance to CM, additional evaluations of CM component-IgE are definitely needed.

Meanwhile, the possibility of adverse reactions to CM in patients who are CM-IgE(–) supports the notion that CM component-IgE measurements should be included to clearly identify CM allergies. In this study, 7.3% of patients who were CM-IgE(–) were sensitized to CM component-IgE, while 38.1% had adverse (broad and suspected IgE-mediated) reactions to dairy foods. Positive correlations between the level of CM-IgE and CM component-IgE were also demonstrated in this study. Cas-IgE was positively correlated with CM-IgE, and this correlation was even stronger than that for ALA-IgE or BLG-IgE and CM-IgE.

In conclusion, we suggest that clinicians screen for CM component-IgE, especially Cas-IgE, with CM-IgE to identify the causative food and then perform follow-up studies to more precisely predict the clinical progress of patients at risk of CM allergy.

REFERENCES

1. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, Sigurdardottir ST, Lindner T, Goldhahn K, Dahlstrom J, McBride D,

Madsen C. The prevalence of food allergy: a meta-analysis. J Allergy Clin Immunol 2007;120:638-46.
2. Bock SA, Sampson HA. Evaluation of food allergy. In: Leung DY, Sampson HA, Geha R, Szefler SJ, editors. Pediatric allergy: principles and practice. 2nd ed. Philadelphia (PA): Saunders; 2010. p. 477-86.
3. Oh JW, Pyun BY, Choung JT, Ahn KM, Kim CH, Song SW, Son JA, Lee SY, Lee SI. Epidemiological change of atopic dermatitis and food allergy in school-aged children in Korea between 1995 and 2000. J Korean Med Sci 2004;19:716-23.
4. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. Pediatrics 1987;79:683-8.
5. Høst A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. Allergy 1990;45:587-96.
6. Järvinen KM, Beyer K, Vila L, Chatchatee P, Busse PJ, Sampson HA. B-cell epitopes as a screening instrument for persistent cow's milk allergy. J Allergy Clin Immunol 2002;110:293-7.
7. Wal JM. Cow's milk allergens. Allergy 1998;53:1013-22.
8. Sicherer SH, Sampson HA. Cow's milk protein-specific IgE concentrations in two age groups of milk-allergic children and in children achieving clinical tolerance. Clin Exp Allergy 1999;29:507-12.
9. Hill DJ, Firer MA, Ball G, Hosking CS. Natural history of cows' milk allergy in children: immunological outcome over 2 years. Clin Exp Allergy 1993;23:124-31.
10. Docena GH, Fernandez R, Chirdo FG, Fossati CA. Identification of casein as the major allergenic and antigenic protein of cow's milk. Allergy 1996;51:412-6.
11. Tabar AI, Alvarez MJ, Echechipía S, Acero S, Garcia BE, Olaguíbel JM. Anaphylaxis from cow's milk casein. Allergy 1996;51:343-5.
12. Shin MY, Han YS, Park HY, Ahn YH, Chung EH, Ahn KM, Lee SI. Cow's milk protein-specific IgE concentrations in two age groups of children with cow's milk allergy. Pediatr Allergy Respir Dis 2004;14:207-14.
13. Chatchatee P, Järvinen KM, Bardina L, Beyer K, Sampson HA. Identification of IgE- and IgG-binding epitopes on alpha(s1)-casein: differences in patients with persistent and transient cow's milk allergy. J Allergy Clin Immunol 2001;107:379-83.
14. Wang J, Lin J, Bardina L, Goldis M, Nowak-Wegrzyn A, Shreffler WG, Sampson HA. Correlation of IgE/IgG4 milk epitopes and affinity of milk-specific IgE antibodies with different phenotypes of clinical milk allergy. J Allergy Clin Immunol 2010;125:695-702.
15. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol 2001;107:891-6.
16. García-Ara C, Boyano-Martínez T, Díaz-Pena JM, Martín-Muñoz F, Reche-Frutos M, Martín-Esteban M. Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant. J Allergy Clin Immunol 2001;107:185-90.
17. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1980;59:44-7.
18. Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. J Pediatr 1988;113:447-51.
19. Sampson HA, Metcalfe DD. Food allergies. JAMA 1992;268:2840-4.
20. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. Pediatrics 1998;101:E8.
21. Byrne AM, Malka-Rais J, Burks AW, Fleischer DM. How do we know when peanut and tree nut allergy have resolved, and how do we keep it resolved? Clin Exp Allergy 2010;40:1303-11.
22. Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: resolution and the possibility of recurrence. J Allergy Clin Immunol 2003;112:183-9.
23. Sampson HA. Food allergy--accurately identifying clinical reactivity. Allergy 2005;60 Suppl 79:19-24.
24. Boyano-Martínez T, García-Ara C, Pedrosa M, Díaz-Pena JM, Quirce S. Accidental allergic reactions in children allergic to cow's milk proteins. J Allergy Clin Immunol 2009;123:883-8.
25. Gern JE, Yang E, Evrard HM, Sampson HA. Allergic reactions to milk-contaminated "nondairy" products. N Engl J Med 1991;324:976-9.
26. Vereda A, van Hage M, Ahlstedt S, Ibañez MD, Cuesta-Herranz J, van Odijk J, Wickman M, Sampson HA. Peanut allergy: clinical and immunologic differences among patients from 3 different geographic regions. J Allergy Clin Immunol 2011;127:603-7.
27. Kramer MS. Breastfeeding and allergy: the evidence. Ann Nutr Metab 2011;59 Suppl 1:20-6.
28. Boyce JA, Assa'a A, Burks AW, Jones SM, Sampson HA, Wood RA, Plaut M, Cooper SF, Fenton MJ, Arshad SH, Bahna SL, Beck LA, Byrd-Bredbenner C, Camargo CA Jr, Eichenfield L, Furuta GT, Hanifin JM, Jones C, Kraft M, Levy BD, Lieberman P, Luccioli S, McCall KM, Schneider LC, Simon RA, Simons FE, Teach SJ, Yawn BP, Schwaninger JM; NIAID-sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-Sponsored Expert Panel Report. Nutrition 2011;27:253-67.