

IgE-Mediated Cow's Milk Allergy: Skin Prick Test Subtypes and Clinical Phenotypes Using Cow's Milk Hydrolysate Infant Formulas

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ABSTRACT

In 1986, Hill (Australia) classified group 1 children with cow's milk allergy (CMA) as having rapid onset, IgE-mediated reactions. In 1989, Schwartz (Rochester, NY) subtyped group 1 children ($n = 75$) into 1A, 1B, and 1C based on skin prick tests (SPTs) to non-hydrolyzed (CM—Similac[®]) and hydrolyzed CM infant formulas (Good Start[®]—partially hydrolyzed; Nutramigen[®]—extensively hydrolyzed). Our objective was to test the hypothesis that SPT subtypes 1A, 1B, and 1C represent different clinical phenotypes. Children with group 1 CMA ($n = 170$) were evaluated between 1989 and 2000. Clinical data analyzed included SPT subtype, signs, and symptoms after CM ingestion, age of onset, presence of other atopic conditions, serum CM-specific IgE, total serum IgE, and follow-up SPTs. Compared to 1A ($n = 82$), 1B ($n = 58$), and 1C ($n = 30$) had higher rates ($p < 0.001$) of systemic reactions to CM, higher ($p < 0.001$) serum-specific IgEs to CM proteins (α -lactalbumin, β -lactoglobulin, casein), higher prevalences of recurrent wheezing/asthma (1A = 23%, 1B = 41%, 1C = 57%; $p < 0.001$), and were 2.34 and 4.34 times more likely to have physician-diagnosed asthma. Prevalence of atopic dermatitis and mean total serum IgE were not significantly different. IgE-mediated CMA frequently is the first clinically identifiable allergic event in early life. SPT with CM and CM-hydrolysate infant formulas classifies these children into three SPT subtypes (1A, 1B, 1C) and two clinical phenotypes. 1A are “topical immediate reactors”—mild reactions, predominantly limited to contact urticaria and/or emesis. 1B and 1C, called “systemic reactors,” are more highly sensitized and clinically reactive—generalized urticaria, angioedema, rhinitis, cough, stridor, and have an increased risk of asthma. Including CMA SPT subtypes and clinical phenotypes in future genetic studies might be informative in sorting out the relationships of the environment and child development to the phenotypic spectrum of asthma. (Pediatr Asthma Allergy Immunol 2003; 16[2]:67–76.)

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INTRODUCTION

IN 1986, HILL AND HIS COLLEAGUES described 100 children in Australia who were unable to tolerate cow's milk (CM) and classified these children with cow's milk allergy (CMA) into three groups based on the nature and timing of their adverse reactions. Group 1 children, designated "immediate reactors," had rapid reactions following ingestion of small amounts of CM. Their reactions were IgE-mediated, consisting mainly of urticaria and angioedema. Group 2 children had mainly gastrointestinal symptoms, occurring after 45 min. Group 3 children had chronic symptoms and a 24-h interval between CM ingestion and the onset of symptoms.⁽¹⁾

In 1989, Schwartz described 75 group 1 children (Rochester, NY) and subclassified them into subtypes 1A, 1B, and 1C, based on immediate skin prick test (SPT) reactions to infant formulas. Children in 1A had positive skin prick tests to CM (Similac®) but negative reactions to partially and extensively hydrolyzed CM protein formulas (Good Start® and Nutramigen®). Those classified as 1B had positive reactions to Similac® and Good Start® but negative reaction to Nutramigen®. Subtype 1C children had positive reactions to all three infant CM formulas.

In the current study, we further investigated the SPT subtypes of an additional 170 children with IgE-mediated CMA seen between 1989 and 2000. We again describe a method of SPT as an alternative to testing with only CM. We believe that testing with CM and hydrolysate formulas is simple, safe, and estimates the degree of sensitization otherwise made possible only by obtaining allergen-specific IgE levels. In addition, we have verified that the subtypes determined by SPT represent different clinical phenotypes. We found that the prevalence of physician-diagnosed asthma is very high in children with IgE-mediated CMA. This is especially true in types 1B and 1C. We propose that further genetic studies of subtypes 1A, 1B, and 1C will lead to a clearer understanding of the relationships between atopy, food sensitization, and the development of asthma.

MATERIALS AND METHODS

Patient population

The study population consisted of 170 children (males = 104, females = 66; mean age = 26.2 months) with IgE-mediated CMA, evaluated between 1989 and 2000 by one author (R.H.S.) in his private pediatric allergy and immunology practice (Allergy, Asthma, Immunology of Rochester, P.C.).^(3,4)

SPT with CM and CM-hydrolysate infant formulas and tests for specific IgE to CM, casein, and whey proteins (α -lactalbumin, β -lactoglobulin) became a routine part of the evaluation and management of CMA in 1989, soon after it was reported that some highly sensitized infants with IgE-mediated CMA had anaphylactic reactions to both partially hydrolyzed whey and extensively hydrolyzed casein "hypoallergenic" infant formulas. It was apparent that others with less severe CMA were able to tolerate the partially hydrolyzed formulas.^(2,3,12) In all instances, parents were informed by R.H.S. and consented to testing.

The practice's database was searched using the diagnosis of "food allergy." Patient charts captured by this search were reviewed. Inclusion criteria for chart review included IgE-mediated CMA indicated by a history obtained from the mother that her infant had an immediate (within 60 min) adverse reaction to CM, supported by positive SPT to CM; documented history that included details of the patient's initial reaction to CM; SPT to Similac®, Good Start®, and Nutramigen® performed at the initial office visit. Children had been referred by their primary care physicians because they had had one or more obvious immediate adverse reactions when fed CM. All of the children had been previously breastfed and had reactions with their first CM feeding. Children with SPT-negative CM-induced acute enterocolitis syndrome were not included.

Skin prick testing

SPTs to Similac® (CM equivalent—Ross Laboratories), Good Start® (partially hydrolyzed whey infant formula—Carnation, Nestle), Nutramigen® (extensively hydrolyzed casein infant formula—Mead Johnson), histamine control (Histrol, histamine phosphate 2.75 mg/mL, Center Laboratories, Port Washington, NY),

and diluent control (Hollister Stier, Division of Miles Laboratories, Inc., Elkhart, IN) were placed on the patients' backs. The infant formulas were prepared as directed on the can for feeding infants and used without further dilution.^(2,3) Aliquots were frozen at -4°C and thawed prior to testing each infant. Whole cow's milk (CM) 1:20 wt/vol (Hollister-Stier) was also used. All patients with positive SPTs to Similac[®] also had positive SPT to CM with wheals and flares of equivalent size. No patients were SPT positive to CM but not to Similac[®]. Tests were read after 10–15 min. An SPT was considered positive if the wheal was ≥ 3 mm in greatest diameter and as large or larger than the wheal of the positive histamine control. All positive wheal reactions had surrounding flare reactions. Wheal and flare diameters were measured and recorded but are not reported in this paper. Some of the reactions were quite large (wheals up to 30×35 mm with pseudopods), requiring topical hydrocortisone and/or oral diphenhydramine for patient comfort. There were no systemic reactions.

Serum-specific IgE levels

Allergen-specific serum IgE concentrations to cow's milk, α -lactalbumin, β -lactoglobulin, and casein were included in the study if they were obtained within 30 days of SPT. Blood samples were obtained by venipuncture and sent to Strong Memorial Hospital Central Laboratories. They were analyzed by the Pharmacia RAST or the Pharmacia CAP System FEIA using standardized allergens and calibrated against the World Health Organization IgE standard. In calculating means, concentrations of <0.35 IU/mL were tabulated as 0.01 and values of >100 IU/mL were tabulated at equal to 100.

Determination of other atopic disorders

Patients were determined to have other atopic disorders by the following criteria: asthma—at the time of initial evaluation the patient had a history of more than one episode of wheezing responding to bronchodilators; food sensitivity—patient had a history of a convincing immediate reaction to a food other than milk and/or had positive SPT to egg, peanut, soy or wheat; allergic rhinitis—patient had a history consistent with the diagnosis which was supported by either positive skin or allergen-specific IgE testing; atopic dermatitis—patient had a physical exam consistent with atopic dermatitis or a history of physician (pediatrician)—diagnosed atopic dermatitis.

Statistical analysis

Chi-square testing was utilized for calculating prevalence of symptoms and atopic disorders. While comparing the prevalence of atopic disorders, each calculation was controlled for the presence of other atopic disorders. For each symptom and atopic disorder that had a significant result, regression analysis was performed to determine the odds ratio. Analysis of variance (ANOVA) was utilized to compare serum specific and total IgE levels between subtypes when patients were divided into three subtypes. Repeated measures analysis was utilized to compare mean specific-IgE levels between CM proteins. Since the specific-IgE data is not normally distributed, a log transformation of the data was done to create a normally distributed dataset for analysis.

RESULTS

Skin prick testing

Patients were classified as type 1A if they had positive SPT reactions to Similac[®] but negative reactions to Good Start[®] and Nutramigen[®]. They were type 1B if they had positive reactions to Similac[®] and Good Start[®] but negative reaction to Nutramigen[®], and they were 1C if they had positive reactions to all three infant formulas. Of the 170 patients, 82 were 1A, 58 were 1B, and 30 were 1C at the time of initial evaluation. No patient had a positive test to Nutramigen[®] and negative test to CM or Good Start[®]. Likewise, no patient had a positive test to Good Start[®] and a negative test to Similac[®] (Table 1).

TABLE 1. DISTRIBUTION OF PATIENTS BY SPT SUBTYPE

<i>SPT type</i>	<i>Number of patients</i>	<i>Male</i>	<i>Female</i>	<i>Mean age at initial evaluation (months)</i>	<i>Age range at initial evaluation (months)</i>	<i>Mean age at first reaction to CM (months)</i>	<i>Age range at time of first reaction (months)</i>
1A	82 (48%)	44	38	22.4	4–140	6.6	1–13
1B	58 (34%)	39	19	25.1	4–162	7.1	1–18
1C	30 (18%)	21	9	39.7	8–172	5.7	1–12
All patients	170	104	66	26.2	4–172	6.0	1–18

Prevalence of reactions

For this study, we defined a systemic reaction as generalized urticaria, angioedema, or any respiratory symptom such as cough, stridor, wheezing, rhinorrhea, nasal congestion, eye tearing, and conjunctival pruritis and injection. We believe that CMA-induced emesis represents a topical reaction of the GI system, which is similar to contact urticaria in the cutaneous system. We evaluated the symptoms that the patient suffered the first time they had a reaction to CM. Chi-square testing showed a significant difference in all of these categories (Table 2).

Odds ratios of reactions

For the symptoms that had a significant difference by chi-square testing, regression analysis was performed to determine the odds ratios. Compared to 1A, patients in 1B had an odds ratio of 4.40 for generalized urticaria, 3.87 for angioedema, 6.20 for respiratory symptoms, and 0.141 for presenting with contact urticaria only. Also compared to 1A, patients in 1C had an odds ratio of 6.30 for generalized urticaria, 10.27 for angioedema, 10.52 for respiratory symptoms, and 0.071 for presenting with contact urticaria only. The calculations for the odds ratios were controlled for the presence of the other mentioned atopic disorders.

Specific IgE results

For each CM protein studied, we attempted to determine if there is a significant difference between mean serum-specific IgE concentrations for the different SPT subtypes. To be included, the specific-IgE studies had to be drawn within 90 days of a skin testing for CM and the patients initial evaluation. Of note, our values are presented as IU/mL. Sampson and others have reported specific IgE values as kU_A/L.⁽⁵⁾

TABLE 2. PREVALENCE OF SYMPTOMS CLASSIFIED BY PATIENTS' INITIAL SKIN TESTING

<i>Symptom</i>	<i>All patients</i>	<i>1A</i>	<i>1B</i>	<i>1C</i>	<i>P-value for chi-square</i>
Contact urticaria	0.83	0.81	0.83	0.90	0.317
Generalized urticaria	0.27	0.12	0.38	0.47	<0.001
Emesis	0.51	0.52	0.45	0.60	0.382
Eczema exacerbation	0.10	0.10	0.12	0.07	0.722
Colic	0.04	0.09	0.0	0.0	0.020
Angioedema	0.28	0.11	0.36	0.60	<0.001
Respiratory symptoms ^a	0.34	0.12	0.48	0.67	<0.001
Contact urticaria only	0.45	0.71	0.26	0.13	<0.001

^aCough, stridor, wheezing, rhinorrhea, nasal congestion, eye tearing, and conjunctival pruritis and injection.

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TABLE 3. INITIAL SPECIFIC IgE VALUE MEANS AND RANGES BY SPT TYPE (ALL VALUES ARE REPORTED AS IU/mL)

<i>Protein</i>	<i>All patients</i>		<i>1A</i>		<i>1B</i>		<i>1C</i>	<i>P-value for ANOVA test (using log transformed values)</i>
α -Lactalbumin	4.55	0.77	0.01–5.94	5.79	0.01–44.0	14.77	0.01–58.6	<0.001
β -Lactoglobulin	3.99	0.89	0.01–4.67	4.20	0.01–44.0	11.88	0.50–37.8	<0.001
Casein	7.57	1.81	0.01–15.30	7.34	0.01–44.0	23.98	0.62–96.1	<0.001
Whole milk	10.51	2.75	0.01–19.90	11.41	0.01–43.3	36.35	1.09–100.0	<0.001

In the study, 99/170 patients had specific-IgE determinations that qualified. This included 48/82 patients in type 1A, 35/58 in type 1B, and 16/30 in type 1C (Table 3). To compare the means of types 1A, 1B, and 1C, ANOVA was performed. This demonstrated a significant difference with a $p < 0.001$.

We had 170 samples that included specific-IgE to whole milk that were obtained within 90 days of skin testing. This included 84 in type 1A, 57 in 1B, and 29 in 1C. In type 1A, 30/84 (36%) had levels ≥ 2.5 IU/mL, and 5/84 (6%) had levels ≥ 15 IU/mL, cutoffs published by Garcia-Ara and Sampson, respectively.^(5,6) In type 1B, 36/57 (63%) had levels ≥ 2.5 IU/mL, and 14/57 (25%) had levels ≥ 15 IU/mL. In type 1C, 27/29 (93%) had levels ≥ 2.5 IU/mL, and 20/29 (69%) had levels ≥ 15 IU/mL.

To determine if one milk protein had significantly higher specific IgE values than the others, the mean specific-IgE values for the three proteins were compared within each subtype. For analytical purposes, values were included only if the patient had specific-IgE levels drawn for all three proteins simultaneously. The mean for casein was higher than the other two proteins. However, this achieved statistical significance only for 1A ($p = 0.013$) and 1C ($p = 0.030$; Table 4).

We had 117 serum samples that included specific IgE values to all three milk proteins drawn simultaneously and within 90 days of skin testing. The 117 samples consisted of 51 from subtype 1A, 43 from 1B, and 23 from 1C. In 71/117 samples (61%), casein had the highest specific IgE value. In type 1A, casein was the highest specific IgE value in 28/51 (55%) of the serum samples. Casein was also the highest value in 23/43 (53%) of the samples from 1B and 20/23 (87%) of the samples from 1C.

Total serum IgE

There were 133 samples of total serum IgE with a mean value of 208.3 IU/mL. This included 63 from patients in subtype 1A, 47 from 1B, and 23 from 1C. The means by SPT type were as follows: 1A = 189.4 IU/mL, 1B = 220.3 IU/mL, and 1C = 240.0 IU/mL. By ANOVA testing, there was no significant difference between the values.

Prevalence of other atopic conditions

See Table 5 for the prevalence of other atopic conditions among our patients at the time of initial evaluation.

TABLE 4. COMPARING INITIAL SPECIFIC IgE MEANS BETWEEN THE THREE CM PROTEINS WITHIN EACH SPT TYPE (ALL VALUES ARE REPORTED AS IU/mL)

<i>Subtype</i>	<i>α-Lactalbumin</i>	<i>β-Lactoglobulin</i>	<i>Casein</i>	<i>P-value for repeated measures analysis (using log transformed values)</i>
All patients	4.55	4.04	9.11	<0.001
1A	0.77	0.90	2.04	0.013
1B	5.79	5.71	10.51	0.178
1C	14.77	11.05	30.32	0.030

TABLE 5. PREVALENCE OF ATOPIC DISORDERS BY SPT TYPE

<i>Atopic disorder</i>	<i>All patients</i>	<i>1A</i>	<i>1B</i>	<i>1C</i>	<i>P-value for chi-square</i>
Asthma	0.35	0.23	0.41	0.57	<0.001
Other food sensitivities	0.50	0.50	0.47	0.57	0.667
Seasonal or perennial allergic rhinitis	0.25	0.21	0.29	0.30	0.417
Atopic dermatitis	0.39	0.32	0.41	0.23	0.133

Odds ratio for asthma/recurrent wheezing

Regression analysis was utilized to compare the prevalence of asthma among the SPT subtypes. When compared to patients in 1A, patients in 1B and 1C were 2.34 and 4.34 (respective odds ratios) more likely to have had physician-diagnosed asthma at the time of initial evaluation.

The mean age of patients with asthma was 33.8 months compared to a mean age of 22.3 months for patients who did not have asthma. In subtype 1A, the respective mean ages were 33.5 and 19.0 months. In 1B, the respective mean ages were 25.0 and 26.6 months. In 1C, they were 46.4 and 27.2 months.

Changes in SPT subtype over time

In the study, 102/170 patients had at least one follow-up visit, which included repeat SPT to all three milk proteins (Table 6).

DISCUSSION

CMA is the most common food allergy in childhood. Prevalence rates between 0.3% and 7.5% have been reported in prospective studies.⁽⁷⁻¹¹⁾ It is probable that both genetic and environmental factors determine the onset and outcome of CMA.

TABLE 6. EVALUATION OF SPT TYPE AT FINAL FOLLOW-UP

<i>Initial SPT type</i>	<i>Mean length of follow-up (months)</i>	<i>Range of follow-up (months)</i>	<i>Standard deviation (months)</i>	<i>Number of patients</i>	<i>Allergy subtype at final SPT</i>
1A	29.3	3-104	25.5	36	Negative 8 1A 22 1B 4 1C 2
1B	39.8	2-106	30.9	44	Negative 4 1A 14 1B 16 1C 10
1C	55.7	12-125	36.1	22	Negative 0 1A 3 1B 6 1C 13

We have presented our experience with 170 infants and children with IgE-mediated CMA, demonstrating that they can be categorized into three subtypes (1A, 1B, 1C) based on SPT with Similac® (whole CM), Good Start® (partially hydrolyzed whey formula), and Nutramigen® (extensively hydrolyzed casein formula). They can be distinguished by the nature of presenting symptoms, levels of specific-IgE to CM proteins, and prevalence of physician-diagnosed asthma. Furthermore, we have shown that these SPT subtypes are independent of total serum IgE levels.

The rationale for classifying children with group 1 IgE-mediated CMA into three SPT subtypes (1A, 1B, 1C) is supported by several of our previous observations. Type 1A children were able to tolerate a partial whey hydrolysate (Good Start®) without becoming further sensitized; all of them tolerated Nutramigen.⁽¹²⁾ Most 1C children did not tolerate Good Start®, and some developed anaphylaxis when fed extensively hydrolyzed casein hydrolysate formulas (Nutramigen® or Alimentum®).⁽¹³⁾ By immunoblotting for specific IgE to CM proteins, serum from 1C children reacted most intensely to alpha-casein.⁽¹⁴⁾ Subtypes could also be distinguished by their relative level of specific-IgE antibodies to CM proteins, including alpha-lactalbumin, beta-lactoglobulin, and casein. Lastly, children in 1B and 1C are least likely to outgrow their CMA; we have identified young adults with group 1B and 1C symptomatic IgE-mediated CMA.⁽¹⁵⁾ Thus, at one end of the spectrum, 1C (systemic reactors) produced high serum levels of CM specific IgE and were clinically very sensitive and at risk. At the other end of the spectrum, 1A (topical reactors) were sensitive but clinically had a milder condition. Characteristics of the population as a whole (1A, 1B, 1C) included the following: (1) almost all of the infants had been exclusively breastfed from birth to the time of their first immediate reaction to CM, (2) the diagnosis was usually made by the infant's mother because of the temporal relationship of CM feeding to the onset of symptoms, and (3) the patients were not primarily referred because they have atopic dermatitis.^(3,4)

In the current study, there is an obvious correlation between CM SPT subtypes and prevalence of systemic symptoms. There are two factors that limit our ability to extrapolate these findings to all patients with CMA.

First, a selection bias exists in our study. All patients were referred to a pediatric allergist by their primary care physician. Perhaps many physicians are comfortable managing CMA without a specialist referral. Therefore, patients referred to an allergist might have a more severe sensitivity. This bias may have affected the distribution of patients by SPT subtype. In a population of all patients with CMA, one may expect more patients to fall into subtype 1A. However, our findings are similar to a recent study by Giampietro et al. They skin tested 32 children with a positive skin test to CM to "hypoallergenic" formulas and found that 19% (6/31) had a positive test to an extensively hydrolyzed formula (Nutrilon Pepti®).⁽¹⁶⁾ This is similar to our findings that 18% were SPT positive to Nutramigen®, also an extensively hydrolyzed preparation.

Second, there was a time delay between the average age of initial reaction and our initial evaluation. Most patients simply practiced avoidance initially and were referred at a later time. Typically, a consultation referral was initiated for one of two reasons. Either the patient had additional acute reactions to CM ingestions or the parents wanted to know if and when they could reintroduce CM into the diet. This phenomenon could lead to another selection bias. Patients who continue to have allergic reactions to CM after a couple of years are likely to have a more severe sensitivity. Furthermore, during this lag time a patient's skin test responses and degree of sensitivity may have changed. Despite these limitations, we believe that our evidence supports the hypothesis that IgE-mediated CMA can be subdivided into two distinct clinical phenotypes identified by SPTs. A prospective, case-control matched study might further support these findings.

For each SPT subtype, the mean specific-IgE level for casein was significantly higher than the means for α -lactalbumin and β -lactoglobulin. This supports the current belief that casein is the most allergenic protein in CM. For patients that were in subtype 1C at the time the labs were drawn, 87% of the results had a casein value that was greater than the others. Thus, children who are clinically more allergic to CM tend to have a sensitivity predominantly to casein.

We believe that our protocol for SPT is helpful in management of children with CMA. In previous work, one of the authors (R.H.S.) performed double-blind, placebo-controlled oral challenges of patients in all three SPT subtypes. When the challenges were performed using Carnation Good Start®, a partially hydrolyzed CM formula, 13/13 patients in 1A tolerated the challenge without any reaction. In 1B 5/8 and 0/5

in 1C tolerated this challenge. The patients who did react to the Good Start® (3/8 in 1B, 5/5 in 1C) experienced either generalized urticaria or respiratory symptoms.⁽¹²⁾ In the current cohort of children in 1A, all of them were able to tolerate Good Start® in supervised open oral challenges and trials (data not presented). Therefore, it is our experience that children in 1A can be offered Good Start® in their diets as a CM alternative and tolerate it without adverse reaction. Without further testing, we believe that it is safest for children in subtypes 1C who are SPT negative to soy to receive a soy-based formula rather than an extensively hydrolyzed CM formula. This recommendation is supported by the observation that some children in 1C have had anaphylactic reactions to extensively hydrolyzed CM-based formulas such as Nutramigen® and Alimentum®, as previously demonstrated by our group using double-blind-placebo-controlled oral challenges.⁽¹³⁾

The mainstay for the diagnosis of CMA is the clinical history supported by positive immediate SPTs and/or specific IgE levels. Although the double-blind-placebo-controlled food challenge (DBPCFC) is the gold standard used for research purposes and to sort out the complexities of perceived multiple food sensitivities, the time- and labor-intensive nature of DBPCFC renders it impractical for general use in clinical medicine. Approximately 80%, but not all children with CMA, become tolerant to CM by 3 years of age.⁽⁹⁾ Therefore, it is clinically helpful for doctors and parents, at the time of diagnosis, to be able to assess not only the magnitude of clinical sensitivity but also to identify those children who may never become tolerant or who may take many years to do so. At some safe point in time, a formal open oral challenge under medical supervision will need to be done to determine if tolerance has developed.

Our protocol for SPT minimizes the need for oral challenges in select patients. Sampson et al. have made recommendations on when to perform an oral milk challenge.⁽⁵⁾ If milk-specific IgE level is 15 kU_A/L or higher, it is greater than 95% (positive predictive value) likely that a child would experience a positive reaction. If the milk-specific IgE level was <15 kU_A/L but ≥0.35 kU_A/L, they suggest that the physician would need to perform some form of milk challenge to determine whether the child is truly reactive to milk. However, Garcia-Ara et al., in their prospective study of 170 children referred to their clinic with a diagnosis suggestive of CMA, showed that 2.5 kU_A/L had a positive predictive value of 90% and 5 kU_A/L had a positive predictive value of 95%. They recommended that, if values are 2.5 kU_A/L or greater, the challenge test should not be performed because of its high positive predictive value (90%).⁽⁶⁾ In subtype 1C, 27/29 patients had specific IgE levels to whole milk that were ≥2.5 IU/mL. According to Garcia-Ara's work, 90% of these patients would have a positive challenge to CM. Thus, in this subtype one could defer the oral challenge until the patient's subtype had changed to 1A or 1B. Consequently, this would decrease not only the inherent risk of anaphylaxis associated with oral challenges but also the cost.

Chatchatee et al., from Sampson's group, proposed that a pattern of epitope recognition is associated with the natural history of CMA. They studied serum from two select, non-randomized groups of patients. Group A (*n* = 9) patients with "persistent" CMA were older than 9 years of age (9–17 years) and had milk-specific IgE (CAP System FEIA) ranging from 60 to >100 kU/L. Group B (*n* = 8) patients were younger than 3 years of age and had specific IgE of <30 kU/L (median = 18.6 kU/L). Group B were considered "likely to outgrow their milk allergy," although this had not been demonstrated prospectively. They studied IgE- and IgG-binding to SPOTs of 96 overlapping as1-casein decapeptides. Two IgE-binding regions, AA 69–78 and AA 173–194, were recognized by the majority of group A persisters (67% and 100%) but by none of the group B children who "are likely to outgrow CMA." There were no differences in IgG binding. The authors concluded that screening for IgE to these two epitopes might be useful in identifying children who will have persistent IgE-mediated CMA. Their group A children most resemble our group 1C children. By our classification, our group 1A are most likely to outgrow their CMA and have much lower milk-specific IgE (mean = 2.82 IU/mL) than Chatchatee's group B.⁽¹⁷⁾

One of the most interesting findings in our study is the high prevalence of a history of recurrent wheezing and physician-diagnosed asthma among all patients. At the time of initial evaluation (mean age = 26.2 months), 35% had a diagnosis of asthma made by their primary care physicians and allergy consultant. Halterman recently showed that 9% of children entering kindergarten in Rochester, New York, carried a diagnosis of asthma.⁽¹⁸⁾ Our population had a mean age that was approximately 3 years younger than Halter-

man's group. However, the 35% prevalence of asthma among our population exceeded her prevalence by nearly four-fold. The prevalence of asthma was significantly higher in subtypes 1B and 1C than in 1A. Together, they had an odds ratio of 3.41 compared to subtype A for having asthma.

IgE-mediated CMA is often the first atopic disorder recognized in children. The high prevalence of asthma in the 1C phenotype (57% at 39.7 months), early onset of atopic sensitization (SPTs positive at 6 months), clinical allergic reactions to a ubiquitous food allergen (CM), and prior breastfeeding (almost 100%) as an apparent predisposing environmental risk factor suggest that childhood populations with IgE-mediated CMA are good candidates to further study the epidemiologic and genetic relationships between atopy, CM sensitization, and the development of asthma.

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