

A new score to predict allergic march in patients with IgE-mediated cow milk allergy

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ABSTRACT

Background: Cow milk allergy (CMA) is the most common food allergy in infants. Some patients will express, in the future, other allergic diseases (allergic march).

Objective: To evaluate if a new scoring system could determine the risk of developing allergic march.

Methods: A retrospective observational cohort study of subjects who were immunoglobulin E (IgE) mediated was conducted. We defined a risk score for atopy (RSA), including clinical and laboratory variables. Three risk groups were defined according to the RSA. We defined as dependent variables atopy (one or more allergic diseases) and atopy+ (two or more allergic diseases). A multivariate logistic regression model was created, which included RSA and the type of formula (high-grade extended hydrolyzed formula [EHF] with *Lactobacillus rhamnosus* GG (LGG), high-grade EHF without LGG, and other formulas).

Results: A total of 211 patients were recruited. When we analyzed the risk of atopy+, we found an increased risk for RSA intermediate-risk (odds ratio [OR 2.08] [95% confidence interval [CI], 0.95–4.56) and high-risk (OR 24.74 [95% CI, 6.26–97.73]) groups, and a decreased risk for the subjects fed with high-grade EHF (OR 0.42 [95% CI, 0.20–0.87]) and also in those subjects fed with high-grade EHF plus LGG (OR 0.30 [95% CI, 0.09–0.98]).

Conclusion: RSA is a simple and useful tool to predict the risk of developing other allergic diseases in patients with IgE-mediated CMA.

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Cow milk allergy (CMA) is the most common food allergy in infants and small children. It affects 2% of children < 5 years of age and 0.9% of the general population.^{1–3} CMA has a wide variety of clinical symptoms due to variability in its immunologic mechanism, which may be immunoglobulin E (IgE) mediated or non-IgE mediated.^{4,5} The diagnosis is based on signs and symptoms as well as allergy studies. The criterion standard for the diagnosis is oral food challenge.⁶ Breast milk is the most advisable food for infants with CMA, and the mother should be encouraged to continue with breast-feeding.^{6,7} Extensively hydrolyzed formulas based on cow milk proteins (CMP) represent an alternative. By definition, these formulas should contain peptides < 3000 kDa⁸ and be well tolerated by at least 90% of patients with confirmed CMA.⁹ However, only some formulas meet these requirements.¹⁰ Some researchers recommend that extensive hydrolyzed formula (EHF) contain mostly peptides < 1000 kDa to prevent allergic reactions.⁷ Soy-based formulas are less expensive^{6,7} and generally well tolerated by in-

fants with CMA, but scientific societies (AAP and ESPGHAN) recommend using EHF instead of soy overall in infants < 6 months of age.^{11,12}

Most children with non-IgE-mediated CMA achieve tolerance before 2 years of age,¹³ whereas most children with IgE-mediated CMA achieve tolerance later, with a wide variability according to different studies.^{13–16} Factors that may influence the development of tolerance were described, including specific IgE levels at diagnosis,^{14,16,17} a decrease in specific-IgE levels^{15,18} and co-occurrence of other allergic diseases: atopic dermatitis,⁶ other food allergies,⁶ asthma, and allergic rhinitis.^{7,15} Some researchers have maintained that CMA is an early manifestation of a genetic predisposition, which may be expressed in the future in the form of other allergic diseases,⁴ known as “allergic march.” Most studies of CMA focused on basic aspects, such as prevention and tolerance, but less information is available about the long-term course of patients. The objective of this study was to describe the onset of allergic diseases in IgE-mediated CMA patients and to evaluate whether new scoring system based on laboratory tests and clinical findings at diagnosis could determine the risk of developing allergic diseases.

METHODS

We conducted a retrospective observational cohort study that was approved by the ethics committee of human investigation at our institution (in accordance

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with the ethical standards laid down in the 1964 Declaration of Helsinki and later amendments). Subjects were recruited from the Pediatric Gastroenterology and Nutrition Unit, Navarra Hospital Complex, a tertiary reference hospital for an estimated population of 640,154 inhabitants.¹⁹ Information of subjects was collected from 1990 to 2013 by performing a recruitment survey and consulting the medical records. The inclusion criteria for the subjects were the following: previously healthy patients with signs and symptoms suggestive of CMA (anaphylactic shock, urticaria, Quincke edema, perioral dermatitis, atopic dermatitis, vomiting, diarrhea, refusal of feedings, spasmodic cough, allergic rhinitis, bronchitis, and other consistent symptoms) and CMP-specific IgE antibodies (IgE specific for casein, β -lactoglobulin or α -lactalbumin; an IgE cutoff point of >0.35 kU/L) on initial assessment. The exclusion criteria were the following: patients with a history of chronic gastrointestinal diseases and patients already diagnosed with IgE-mediated CMA who received previous treatment. Oral food challenge was performed in all the patients except those with a history of anaphylaxis or severe allergic reaction after exposure to CMP or those with very high levels of specific-IgE (>2.5 kU/L) in the initial determination.

Information was collected for the following variables: date of birth, pregnancy tolerance (poor pregnancy tolerance was defined as the presence of any of the following diseases in the mother during pregnancy: hypertension, preeclampsia or eclampsia, threat of miscarriage or premature birth, or gestational diabetes), duration of pregnancy (premature infants were defined as those born with gestational ages of <37 weeks, and full-term infants of ≥ 37 weeks of gestational age), delivery type (variable categorized as vaginal delivery [spontaneous or assisted] or cesarean delivery), formula feeding in the hospital (FFH) (variably categorized as patients who were fed formula in isolated instances during hospitalization on the maternity ward and were later fed exclusively by breast-feeding, and patients who were not fed by any adapted formula), duration of breast-feeding (categorized as breast-feeding for ≥ 6 months or breast-feeding for <6 months), family history of allergy (FHA) (categorized as none, one, and two or more first-degree relatives with a history of allergic disease), age and clinical manifestations at diagnosis, type of formula used (for purposes of analysis, this variable was categorized as vegetable-based formulas, high-grade EHF for those in which $>95\%$ peptides were <1000 kDa, high-grade EHF plus *Lactobacillus rhamnosus* GG (EHF + LGG), low-grade EHF for those with a higher proportion of peptides > 1000 kDa or amino acid-based formulas), eosinophilia at diagnosis (percentage of total leukocytes that were eosinophils), total IgE value at diagnosis, and CMP-specific IgE.

Subsequently, June 2015, was taken as a cross-sectional cutoff point for completion of follow up. At that time, the subjects were reviewed to examine the development of allergic diseases: asthma, atopic dermatitis, allergic rhinitis, and other food allergies (including eggs, fish, nuts, and legumes). A diagnosis of allergic diseases was made in these subjects by their reference pediatrician and/or allergologist by following the usual clinical standards for these pathologies. Continuous laboratory variables were categorized to dichotomous variables by using receiver operating characteristic curve analysis for each laboratory parameter in each outcome variable (atopy, defined as the presence of one allergic disease, and atopy+, defined as the presence of two or more allergic diseases), and cutoff points were selected for each parameter: 8% for eosinophils; 300 kU/L for total IgE value; and 5 kU/L for casein-specific IgE, α -lactalbumin-specific IgE, and β -lactoglobulin-specific IgE values.

Statistical analysis for dichotomous variables was performed by using the Pearson χ^2 test for comparison of proportions. Odds ratios (OR) and 95% confidence intervals (CI) were calculated by using the logistic regression method. By using these data, a score risk of atopy was designed (Table 1). This score was tested for the risk of atopy and atopy+ by using the logistic regression method. Multivariate logistic regression models were built for atopy and atopy+ by using this variable and type of formula feeding (for analytical purposes variable was categorized as a threefold categories variable: high-grade EHF, high-grade EHF + LGG, and other formulas).

RESULTS

A total of 211 subjects were recruited. The sex distribution was 128 boys (60.7%) and 83 girls (39.3%). The mean age at diagnosis was 5.07 ± 2.67 months, and the mean age at the end of follow up was 14.41 ± 5.42 years. A univariate analysis for the different independent variables was performed for atopy and atopy+ in patients with CMA (Table 2). The risk score for atopy (RSA) was developed (Table 1) with clinical and analytical data. The score was tested by receiver operating characteristic curve studies for variable atopy and atopy+. Two cut points were established, resuming the variables into three risk groups: low-risk group (score of <0), intermediate risk group (score of ≥ 0 but <3), and high-risk group (score of ≥ 3). The sensitivity and specificity of the cut points are detailed in Table 3. Univariate analysis of risk groups for atopy was OR 2.04 (95% CI, 0.96–4.35) for intermediate risk and OR 11.52 (95% CI, 2.44–54.37) for high risk. For atopy+, the OR of the intermediate risk was 1.88 (95% CI, 0.88–4.04) and, for high risk was 23.86 (95% CI, 6.16–92.17).

Table 1 Risk score for atopy in subjects with IgE-mediated cow milk allergy

Risk Variable	Score
Mode of delivery	
Caesarean delivery	−1
Vaginal delivery	0
Formula feeding in hospital*	
Yes	−1
No	0
Family history of allergy	
No first-degree relatives	0
1 first-degree relative	1
≥2 first-degree relatives	3
Total IgE value ≥ 300 kU/L	
Yes	2
No	0
Eosinophils ≥ 8%	
Yes	2
No	0
Specific-IgE ≥ 5 kU/L#	
Yes	2
No	0

IgE = immunoglobulin E.

*Subjects who were fed with formula in isolated instances during hospitalization on the maternity ward and were later fed exclusively by breast-feeding.

#One or more specific-IgE antibody levels ≥ 5 kU/L for casein, α-lactalbumin, and β-lactoglobulin.

After univariate analysis of the type of formulas, we decided to categorize the variable in three categories (high-grade EHF, high-grade EHF + LGG, and the other formulas) and then we performed a multivariate analysis, including the RSA and the type of formula used (Table 4). We found an increased risk of atopy for RSA in intermediate- and high-risk groups but a low risk for subjects fed with high-grade EHF. When we analyzed the risk of atopy+, we obtained a similar pattern of increased risk for RSA in intermediate- and high-risk groups, and a decreased risk for subjects fed with high-grade EHF and also in those fed with high-grade EHF + LGG.

DISCUSSION

This study was novel in its examination of perinatal, nutritional, and analytical risk factors, and their impact on the subsequent development of other allergic diseases in patients with CMA. We developed an RSA to help estimate the risk of development of allergic march in patients with CMA. This scoring system was based in clinical and analytical parameters that were previously related to the risk of the development of CMA and other allergic diseases.

The first factor we included in the score was the mode of delivery. Caesarean delivery has been related to the development of CMA^{19,20} and also with the development of other allergic diseases,²¹ but other studies show contradictory results.^{22,23} In our scoring system, caesarean delivery was included with a negative value, the same as the variable FFH. Other studies were of the relationship of FFH with the development of CMA, some studies found a positive association,^{24,25} but others did not find this.^{26,27} In one of our previous studies, we found that both, early and isolated introduction of CMP with a subsequent period of prolonged breastfeeding (BF) and the presumable changes in the intestinal microflora produced by a caesarean delivery act together in the development of CMA, with caesarean delivery being a predisposing factor, whereas FFH would be the trigger.²⁸ Another of our previous studies found that caesarean delivery and FFH were risk factors to develop CMA but did not show increased risk of development of allergic march.²⁹ We think that caesarean delivery and FFH are environmental factors that increase the risk of CMA but not the risk of allergic march. So this group of patients had a better prognosis than those with genetic or familial risk factors. These facts due to the results of univariate analysis explain the negative values in the scoring system for these variables.

Another strongly linked risk factor was a family history of allergy. This has previously been described in the general population.^{30,31} The FHA variable was defined as three groups: none, one, and two or more first-degree relatives with a history of allergic disease. The reason for this categorization was to improve the specificity of the parameter, given the high prevalence of allergic diseases in our population described in one of our previous studies.²⁸ The definition of a family history of allergy as two or more first-degree relatives has previously been used by other researchers in populations with a high prevalence of allergic diseases.³² We also used some laboratory variables that have traditionally been linked to allergic diseases, such as eosinophilia³³ and the total IgE value,³⁴ and also CMP-specific IgE values, which have previously been used for diagnosis and as a predictor of tolerance in patients with CMA.^{6,35}

When we completed the RSA, every subject obtained a numerical value that goes from −2 to 9. Even with a good area under the curve (0,729) for atopy+, there was not a single point with a good sensitivity and specificity, but we established three levels of risk by using the cut points 0 and 3. Those subjects with an RSA ≥ 0 had a higher risk of developing other allergic diseases than those with a negative score, with a good test sensitivity (although a low specificity). Patients with an RSA ≥ 3 have a very high risk of allergic march with an excellent specificity (but a low sensitivity). This

Table 2 Univariate analysis of risk of atopy

	Atopy		Atopy+	
	OR (95% CI)	<i>p</i> (sig.)	OR (95% CI)	<i>p</i> (sig.)
Gender*	1.80 (0.96–3.37)	0.065	1.12 (0.64–1.95)	0.676
PPT#	4.18 (0.95–18.4)	0.058	1.35 (0.57–3.20)	0.489
Duration of pregnancy§	1.19 (0.24–5.95)	0.825	1.17 (0.30–4.51)	0.825
Caesarean¶	0.59 (0.31–1.10)	0.101	0.70 (0.40–1.21)	0.204
FFH	1.31 (0.64–2.66)	0.455	0.64 (0.33–1.25)	0.455
Duration of BF**	1.94 (0.70–5.36)	0.199	0.84 (0.38–1.83)	0.199
FHA		0.462		0.004
1 first-degree member	1.13 (0.56–2.26)	0.730	1.14 (0.61–2.12)	0.665
≥2 first-degree members	1.95 (0.67–5.63)	0.214	5.14 (1.92–13.72)	0.001
Type of formula		0.130		0.096
High-grade EHF	0.29 (0.10–0.81)	0.019	0.54 (0.26–1.15)	0.111
Vegetable formula	0.49 (0.13–1.72)	0.478	0.72 (0.28–1.89)	0.515
Amino-acid formula	1.14 (0.11–11.17)	0.909	2.10 (0.38–11.45)	0.391
High-grade EHF + LGG	0.42 (0.11–1.59)	0.207	0.30 (0.10–0.86)	0.026

Atopy+ = presence of ≥2 allergic diseases; OR = odds ratio; CI = confidence interval; sig. = statistical signification; PPT = poor pregnancy tolerance; FFH = formula feeding in the hospital; BF = breastfeeding; FHA = family history of allergy; EHF = extended hydrolyzed formula; LGG = *Lactobacillus rhamnosus* GG.

*Female gender was used as the reference category.

#The presence of any of the following diseases in the mother during pregnancy: hypertension, preeclampsia and/or eclampsia, threat of miscarriage or premature birth, or gestational diabetes.

§Full-term infants with gestational ages of > 37 wk were used as the reference category.

¶Vaginal delivery was used as the reference category.

||Subjects who were fed formula in isolated instances during hospitalization on the maternity ward and were later fed exclusively by breast-feeding.

**BF for < 6 mo was used as the reference category.

Table 3 Sensitivity and Specificity cut points of RSA

RSA	Atopy		Atopy+	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
≤0	80.91	39.13	85.39	34.09
≥3	24.42	95.65	34.83	96.59

RSA = risk score for atopy; atopy+ = presence of ≥2 allergic diseases.

simple score can help us to predict the risk of allergic march of every patient with CMA by using tools that we use routinely in management of these patients.

We also found that the type of treatment received could determine the subsequent course of these patients. When we classified the different formulas, we divided them into five groups according to their composition: vegetable-based formulas (rice or soy), high-grade EHF for those in which >95% peptides were <1000 kDa, high-grade EHF plus *Lactobacillus rhamnosus* GG (EHF + LGG), low-grade EHF for those with a higher proportion of peptides >1000 kDa, or amino acid-based formulas. Both high-grade and low-grade are EHF and comply with regulations for CMA treat-

ment.^{8,9} We established the two groups because some researchers recommended the use of the high-grade EHF⁷ and overall because our previous study demonstrated differences in the development of allergic march in the high-grade EHF group.²⁹ Also, we make another group with high-grade EHF + LGG, because some recent studies point to a faster tolerance acquisition³⁶ and a reduction in other allergic manifestations³⁷ in patients treated with these formulas.

Finally, for the reduced size of some groups and null differences in the univariate analysis, we decided to merge the remaining groups (vegetable based, amino-acid based, and low-grade EHF). In a multivariate analysis, we found that the subjects treated with high-

Table 4 Multivariate analysis of risk of atopy

	Atopy		Atopy+	
	OR (95% CI)	<i>p</i> (sig.)	OR (95% CI)	<i>p</i> (sig.)
Score risk atopy*		0.005		<0.001
Intermediate risk#	2.25 (1.03–4.92)	0.042	2.08 (0.95–4.56)	0.067
High risk	11.37 (2.36–54.74)	0.002	24.74 (6.26–97.73)	<0.001
Type of formula		0.024		0.032
High-grade EHF	0.32 (0.14–0.74)	0.008	0.42 (0.20–0.87)	0.020
High-grade EHF + LGG	0.67 (0.17–2.54)	0.558	0.30 (0.09–0.98)	0.048

Atopy+ = presence of ≥ 2 allergic diseases; OR = odds ratio; CI = confidence interval; sig. = statistical significance; EHF = extended hydrolyzed formula; LGG = *Lactobacillus rhamnosus* GG.

*The low-risk group was used as the reference category.

#All other formulas were used as reference category.

grade EHF had a lower risk of developing other allergic diseases, and these results are stronger in patients who clearly develop allergic march (atopy+) and in those treated with high-grade EHF + LGG. The pathophysiologic reason is not clear. Perhaps the lower allergenic burden of these high grade EHF may have helped to stop the immune response already activated in these patients, decreasing the risk of developing other allergic diseases. Our observation that children given *Lactobacillus* GG in formula had less risk of developing other allergies was supportive of the concept that the microbiota in the gastrointestinal tract of the infant may significantly influence the immune priming and regulation of the immune response.³⁷ Further studies are needed to better understand the mechanisms involved in these observations.

This study had limitations. It was an observational study over an extended period of time. The variable that we believed could have been most affected by loss to follow-up bias was allergies in relatives in the case of younger siblings who had not yet been born when the data were collected. Another type of bias that may have occurred in collecting data *via* survey was patients over- or underestimating allergic diseases. Even so, the initial sampling showed an excellent level of concordance with the medical records, and the prevalences obtained were consistent with other published series.³⁸ Also, although other food allergies have been studied and registered, aeroallergen sensitization has not been considered or registered like an independent variable in these patients and could be related with allergic march. Missing this variable could make the current results subject to residual confounding.

CONCLUSION

We affirmed that RSA was a simple and useful tool to predict the risk of development of other allergic

diseases in patients with IgE-mediated CMA. Treatment with EHF in which >95% of peptides were <1000 kDa seemed to protect from developing other allergic diseases compared with the use of other formulas, and the addition of LGG seemed to bring a stronger reduction in patients who clearly developed allergic march.

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