Independent predictive factors for the persistence and tolerance of cow's milk allergy

Erdem Topal, MD[1], Mehmet Halil Çeliksoy, MD[2], Mustafa Arga, MD[3], Mustafa Sinan Kaynak[4], Yücel Duman[5], Semih Demirtaş, MD[1], Cem Alataş, MD[1], Hayrettin Tonbul, MD[4], Zeynep Hazıroğlu Ökmen, MD[2] and Huri Maral Dalkılıç, MD[3]

Background: **Cow's milk protein allergy (CMPA) is usually transient, with most children tolerating ingested cow's milk by 3 years of age. This study aimed to determine factors that promote or hindering the development of tolerance to CMPA.**

Methods: **A logistic regression model was used to determine independent risk factors associated with tolerance and persistence of CMPA.**

Result: **A total of 178 children diagnosed with CMPA were included in the study. The patients' median age was 32 months (minimum-maximum, 14 to 144 months), and their median follow-up period was 30 months (minimum-maximum, 12 to 54 months). In the follow-up, CMPA persisted in 62 (34.8%) patients. The patients were divided into 2 groups according to patient's age. Group I was <3 years old and group II was ≥3 years old. The factors independently associated with the persistence of CMPA for group I were as follows: comorbid food allergies ($p = 0.021$), the presence of an immunoglobulin E (IgE)-mediated reaction ($p = 0.001$), and respiratory system symptoms (ie, tachypnea) ($p = 0.036$). The presence of gastrointestinal-related discomfort ($p = 0.001$) was an independent risk factor associated with the development of tolerance. The presence of comorbid food allergies ($p = 0.03$) was the only independent predictive factor for CMPA persistence for group II.**

Conclusion: **The prognosis in cases of CMPA, a food allergy, is good, with tolerance developing over time. The presence of IgE-mediated CMPA, respiratory-related symptoms (ie, tachypnea), and the presence of comorbid food allergies have negative effects on tolerance.** © 2018 ARS-AAOA, LLC.

Key Words:
allergy; cow's milk; persistence; predictive factors; tolerance

***How to Cite this Article*:**
Topal E, Çeliksoy MH, Arga M, et al. Independent predictive factors for the persistence and tolerance of cow's milk allergy. *Int Forum Allergy Rhinol*. 2019;9:67–5.

Introduction

Cow's milk protein allergy (CMPA) is common in infants. The incidence of CMPA during the first year of life is estimated to be 2% to 7.5%.[1–3] It is the most common food allergy in children younger than 3 years[4,5]; the prevalence of CMPA decreases to less than 1% in children 6 years and older.[6] Therefore, CMPA is transient and carries a good prognosis. Symptom severity after cow's milk ingestion,[7] a large wheal response to skin-prick tests and a high specific-immunoglobulin E (IgE) antibody titer to bovine proteins,[8,9] are prognostic factors in CMPA. However, the clinical parameters that contribute to the duration of CMPA and in what order of magnitude remain unclear in pediatrics.

A number of studies have reported that children with non–IgE-mediated reactions to cow's milk recovered earlier than those with IgE-mediated reactions.[6,10,11] One study found that CMPA, in conjunction with other food allergies and asthma, was associated with persistence.[12] The factors that promote the development of tolerance remain unclear.

The aims of the current study were to determine the factors promoting or hindering the development of tolerance to CMPA.

[1]*Faculty of Medicine, Department of Pediatric Allergy and Immunology, Inonu University, Malatya, Turkey;* [2]*Department of Pediatric Allergy and Immunology, GOP Taksim Education and Research Hospital, Istanbul, Turkey;* [3]*Faculty of Medicine, Department of Pediatric Allergy and Immunology, Medeniyet University, Istanbul, Turkey;* [4]*Faculty of Pharmacy, Inonu University, Malatya, Turkey;* [5]*Faculty of Medicine, Department of Microbiology, Inonu University, Malatya, Turkey*

Correspondence to: Erdem Topal, MD, Faculty of Medicine, Department of Pediatric Allergy and Asthma, Turgut Ozal Medical Center, Inonu University, 44280, Malatya, Turkey; e-mail: erdemtopal44@gmail.com

Potential conflict of interest: None provided.
10.1002/alr.22227
View this article online at wileyonlinelibrary.com.

Received: 11 July 2018; Revised: 25 September 2018; Accepted: 26 September 2018
DOI: 10.1002/alr.22227
View this article online at wileyonlinelibrary.com.

Patients and methods

Study design

Patients diagnosed with CMPA who were admitted to the Pediatric Allergy and Immunology Department at 3 teaching and research hospitals (Inonu University Faculty of Medicine, Medeniyet University Faculty of Medicine, and the GOP Taksim Education and Research Hospital) from June 2013 to September 2017 were included in the study. The diagnosis of CMPA was based on the resolution of symptoms upon cow's milk elimination from the children's diet (or the mothers' diets in cases of breastfed children), followed by the return of symptoms on oral challenge with cow's milk or cow's milk formula, depending on the age of the child. Tolerance was based on a negative open oral cow's milk challenge, followed by regular ingestion of age-appropriate quantities of cow's milk at home, without any symptoms. A diagnosis of IgE-mediated CMPA was considered in children who developed allergic symptoms within 2 hours of exposure to cow's milk in an oral food challenge and showed evidence of sensitization to cow's milk as detected by skin-prick test and serum-specific IgE for cow's milk. Non–IgE-mediated CMPA was considered in children in whom typical symptoms developed more than 8 hours after exposure to cow's milk. The children were followed up twice a year until the development of tolerance to CMPA.

All the patients had complete medical records, and these were analyzed to collect demographic and clinical data. The data included age, sex, duration of follow-up, breast feeding at least for 6 months, monthly family income, pets in the home, exposure to cigarettes, a history of co-atopic diseases (atopic eczema, recurrent wheeze, or drug allergies), comorbid food allergies, a history of familial atopic diseases and food allergies, sensitization to food allergens other than cow's milk, type of reaction, clinical manifestations of CMPA, and laboratory findings. Tachypnea and hypotension were evaluated according to the patient's age. A respiratory rate higher than the upper limit according to the patient's age was defined as tachypnea.

The research protocol was approved by the ethics committee of Inonu University Faculty of Medicine. All the participants' parents or guardians provided written informed consent.

Data analysis

Statistical analyses were performed using SPSS software (ver. 15; SPSS Inc., Chicago, IL). Categorical variables were compared using a chi-square test, and quantitative variables were compared using the Mann-Whitney *U*-test. A 2-sided p value < 0.05 was considered to indicate statistical significance. A logistic regression model was constructed. In the model, a multivariate analysis was used, including statistically significant variables from the univariate analyses to identify factors affecting persistence and tolerance after a diagnosis of CMPA.

Results

Demographics

A total of 178 children diagnosed with CMPA were included in the study. Ninety-eight (55.1%) of the patients were males. Their median age was 32 months (minimum-maximum, 14 to 144 months), and the median follow-up period was 30 months (minimum-maximum, 12 to 54 months). In the follow-up, CMPA persisted in 62 (34.8%) patients. Forty-six (25.8%) of the 178 patients had been diagnosed first 6 months of life. One-hundred (56.2%) of the patients had comorbid atopic diseases (recurrent wheezing, 36%; atopic eczema, 33.1%; drug allergies, 2.8%), and 52 (29.2%) had comorbid food allergies other than CMPA (eggs, 82.6%; nuts, 3.8%; legumes, 5.7%; other, 7.6%). In terms of familial diseases, 69 (38.7%) of the children's parents had a diagnosis of atopic disease, whereas 8 (4.5%) parents had been diagnosed with a food allergy. One-hundred and thirty-eight (77.5%) of the patients had been breastfed. Eighteen (10.1%) of the patients had a pet at home, and 65 (36.5%) of the patients had cigarette smoke exposure.

In 114 (64%) cases, the reactions were IgE-mediated. In terms of the patients' clinical symptoms, 128 (71.9%) had cutaneous symptoms (urticaria, 51.1%; pruritus, 33.7%; angioedema, 11.8%), 90 (50.6%) had gastrointestinal system symptoms (vomiting, 21.3%; diarrhea-proctocolitis, 37.6%; discomfort, 20.8%; constipation, 2.8%), 33 (18.5%) had respiratory system symptoms (cough, 11.2%; tachypnea, 11.8%; wheezing, 8.4%; stridor, 2.8%; rhinitis, 2.8%), 15 (8.4%) had anaphylaxis, and 4 (2.2%) had hypotension.

Predictive factors for persistence and tolerance of cow's milk allergy

The patients were divided into 2 groups according to patient's age. Group I was <3 years old and group II was ≥3 years old. In the univariate analyses, the following factors were related to persistence for group I: age at onset of symptoms > 6 months ($p = 0.03$), the presence of comorbid food allergies ($p = 0.04$), an IgE-mediated reaction ($p = 0.001$), the presence of cutaneous-related symptoms ($p = 0.009$), urticaria ($p = 0.03$), the presence of respiratory system symptoms ($p = 0.04$), the presence of tachypnea ($p = 0.02$), and initial serum food-specific IgE level >5 IU/L ($p = 0.01$). The presence of a non–IgE-mediated reaction ($p < 0.001$), the presence of gastrointestinal symptoms ($p = 0.001$), diarrhea-proctocolitis ($p < 0.001$), and discomfort ($p = 0.004$) were risk factors associated with tolerance. The factors that related to persistence for the both group were summarized in Tables 1 and 2. The following factors were independently associated with persistence according to the logistic regression model for group I: the existence of comorbid food allergies ($p = 0.021$), the presence of an IgE- mediated reaction ($p = 0.001$), and the presence of respiratory system symptoms (i.e., tachypnea)

TABLE 1. Comparison of demographics between tolerance group and persistence group by univariate analysis*

Demographics	Group I (children <3 years old)			Group II (children ≥3 years old)		
	Tolerance group (n = 68) n (%)	Persistence group (n = 44) n (%)	*p*	Tolerance group (n = 48) n (%)	Persistence group (n = 18) n (%)	*p*
Gender, male	34 (50)	25 (56.8)	0.60	29 (60.4)	10 (55.6)	0.93
Age of onset of symptoms >6 months	43 (63.2)	36 (81.8)	**0.03**	35 (72.9)	18 (100)	**0.01**
Follow-up duration (months), median (minimum-maximum)	18 (12–42)	18 (18–42)	0.16	42 (18–54)	42 (18–54)	0.35
Other co-atopic diseases	35 (51.5)	23 (52.3)	1.00	34 (70.8)	8 (44.4)	0.09
Family atopy history	27 (39.7)	10 (43.2)	0.86	25 (52.1)	7 (38.9)	0.49
Family food allergy history	4 (5.9)	1 (2.3)	0.64	3 (6.2)	–	NC
Comorbid food allergies	12 (17.6)	15 (34.1)	**0.04**	15 (31.2)	10 (55.6)	0.07
Sensitization to other foods	23 (33.8)	23 (52.3)	0.08	23 (47.9)	11 (61.1)	0.49
Breast feeding ≥ 6 months	49 (73.1)	33 (75)	0.82	41 (85.4)	15 (83.3)	1.00
Monthly income < $1000	39 (59.1)	32 (72.7)	0.20	29 (60.4)	11 (61.1)	0.49
Pet in home	7 (10.3)	5 (11.4)	1.00	4 (8.3)	2 (11.1)	0.66
Exposure to cigarettes	27 (39.7)	16 (36.4)	0.87	18 (37.5)	4 (22.2)	0.37
Clinical symptoms within 2 hours of exposure	37 (54.4)	32 (72.7)	0.05	33 (68.8)	17 (94.4)	0.05
Type of reaction						
IgE-mediated	36 (52.9)	37 (84.1)	**0.001**	29 (60.4)	12 (66.7)	0.85
Non–IgE-mediated	33 (48.5)	7 (15.9)	**0.001**	16 (33.3)	2 (11.1)	0.13
Mix	13 (19.1)	14 (31.8)	0.19	7 (14.6)	4 (22.2)	0.47

*Bold values are significant at $p < 0.05$.
IgE = immunoglobulin E; NC = Non-calculated.

($p = 0.036$). The presence of gastrointestinal-related discomfort ($p = 0.001$) were independent risk factors associated with tolerance (Table 3). The presence of comorbid food allergies (odds ratio [OR], 3.611; 95% confidence interval [CI], 1.088 to 11.984; $p = 0.03$) was the only independent predictive factor for CMPA persistence for group II in the logistic regression model. Also, it was determined that no independent predictive factor related with tolerance in group II.

There was no statistically significant association between tolerance and sex, co-atopic diseases, breast feeding, monthly family income, pets in the house, exposure to cigarette smoke, sensitization to other foods, pruritus, angioedema, flushing, atopic eczema exacerbation, vomiting, constipation, coughs, stridor, wheezing, rhinitis, a reaction within the first 2 hours of exposure, total IgE level, and eosinophilia for both groups ($p > 0.05$) (Tables 1 and 2).

Discussion

There are limited numbers of studies on factors that predict the development of tolerance and persistence for CMPA. The current study showed that IgE-mediated reactions to cow's milk, the presence of respiratory-related symptoms (ie, tachypnea), and the presence of comorbid food allergies were independent factors for CMPA persistence for children <3 years old. The presence of gastrointestinal system–related discomfort was an independent predictor of tolerance development. The presence of comorbid food allergies was the only independent predictive factor for CMPA persistence for the children ≥3 years old.

Previous studies demonstrated that IgE-mediated reactions to CMPA and a high level of serum specific IgE for cow's milk were associated with persistence.[12–14] In parallel with these studies, the presence of an IgE-mediated reaction in our study increased the probability of CMPA persistence 5.6 times for the children <3 years old. Shek et al.[13] reported that individuals with a high level of serum-specific IgE developed tolerance at an older age and that patients whose IgE level decreased rapidly in the follow-up period developed tolerance at a younger age. In the present study, level of specific IgE for cow's milk higher than 5 IU/L in a 1-way analysis was associated with CMPA persistence in the follow up.

TABLE 2. Comparison of clinical symptoms between tolerance group and persistence group by univariate analysis

Clinical symptoms	Group I (children <3 years old)			Group II (children ≥3 years old)		
	Tolerance group (n = 68) n (%)	Persistence group (n = 44) n (%)	*p*	Tolerance group (n = 48) n (%)	Persistence group (n = 18) n (%)	*p*
Cutaneous	42 (61.8)	38 (86.4)	**0.009**	34 (70.8)	14 (77.8)	0.80
Urticaria	25 (36.8)	26 (59.1)	**0.03**	28 (58.3)	12 (66.7)	0.73
Pruritus	20 (29.4)	14 (31.8)	0.952	16 (33.3)	10 (55.6)	0.173
Angioedema	7 (10.3)	3 (6.8)	0.737	7 (14.6)	4 (22.2)	0.474
Flashing	5 (7.4)	3 (6.8)	1.00	6 (12.5)	2 (11.1)	1.00
Atopic eczema exacerbation	13 (19.1)	14 (31.8)	0.191	7 (14.6)	4 (22.2)	0.474
Gastrointestinal	44 (64.7)	14 (31.8)	**0.001**	25 (52.1)	7 (38.9)	0.49
Vomiting	15 (22.1)	3 (6.8)	0.06	15 (31.2)	5 (27.8)	1.00
Diarrhea-proctocolitis	37 (54.4)	9 (20.5)	**0.001**	18 (37.5)	3 (16.7)	0.18
Discomfort	19 (27.9)	2 (4.5)	**0.004**	14 (29.2)	2 (11.2)	0.19
Constipation	3 (4.4)	1 (2.3)	1.00	1 (2.1)	–	NC
Respiratory	5 (7.4)	10 (22.7)	**0.04**	11 (22.9)	7 (38.9)	0.22
Cough	2 (2.9)	6 (13.6)	0.05	7 (14.6)	5 (27.8)	0.28
Tachypnea	3 (4.4)	8 (18.2)	**0.02**	5 (27.8)	5 (50)	0.12
Stridor	–	2 (4.5)	NC	1 (2.1)	2 (11.1)	0.17
Wheezing	4 (5.9)	4 (9.1)	0.71	5 (10.4)	2 (11.1)	1.00
Rhinitis	1 (1.5)	1 (2.3)	1.00	2 (4.2)	1 (5.6)	1.00
Anaphylaxis	1 (1.5)	4 (9.1)	0.07	5 (10.4)	5 (27.8)	0.12
Hypotension	–	–	NC	1 (2.1)	3 (16.7)	0.05
Laboratory						
Total IgE, median (minimum-maximum)	19.4 (2.2–1199)	37 (1.1–1096)	0.10	58.3 (1–2090)	39 (4.6–816)	0.516
Initial food-specific IgE level >5 IU/L	7 (10.3)	13 (29.5)	**0.01**	11 (22.9)	8 (44.4)	0.15
Eosinophil >%4	35 (51.5)	21 (47.7)	0.84	29 (60.4)	12 (66.7)	0.85

*Bold values are significant at $p < 0.05$.
IgE = immunoglobulin E; NC = Non-calculated.

TABLE 3. Logistic regression: potential predictors affecting the persistence and tolerance for cow's milk protein allergy for the group I (children <3 years old)*

Variables	Beta	Odds ratio	95% CI	*p*
Potential predictors of persistence				
Comorbid food allergies	1.173	3.231	1.192–8.759	0.021
IgE-mediated reaction	1.737	5.681	2.045–15.783	0.001
Respiratory system symptom (tachypnea)	1.322	3.751	1.093–12.871	0.036
Potential predictors of tolerance				
Gastrointestinal-related discomfort	1.535	4.642	1.936–11.126	0.001

*Variables in the logistic regression model for persistence: age at onset of symptoms >6 months, other food allergies, IgE-mediated reaction, clinical symptoms within 2 hours of exposure, cutaneous symptoms, urticaria, respiratory symptoms, tachypnea, and an initial serum specific-IgE level for cow's milk >5 IU/L. Variables in the logistic regression model for tolerance: Gastrointestinal symptoms, diarrhea-proctocolitis, gastrointestinal-related discomfort, and non–IgE-mediated reactions.
CI = confidence interval; IgE = immunoglobulin E.

In a univariate analysis, Santos et al.[12] reported that an allergic reaction to CMPA that included dyspnea was associated with persistence, whereas they detected no statistically significant association between these parameters in a logistic regression analysis. On the contrary, in our study, the presence of respiratory system symptoms (ie, tachypnea) was statistically significantly associated with an increased risk of persistence in both the univariate analysis and logistic regression analysis for the children <3 years old. The fact that dyspnea and tachypnea, which develop in the respiratory tract, are easily realized in the examination decreases the risk of missing a diagnosis of CMPA, and IgE-mediated respiratory system symptoms can be explained with this result.

Previous studies showed that a non–IgE-mediated reaction to CMPA led to the development of earlier tolerance.[9,13] In the same studies, patients with proctocolitis were more likely to develop tolerance. In the present study, the existence of gastrointestinal-related discomfort, which is a non–IgE-mediated reaction, increased the development of tolerance 4.6 times. Therefore, the literature and the findings of the present study show that the existence of non–IgE-mediated reactions, such as gastrointestinal system symptoms, to CMPA appear to be associated with the development of tolerance at a younger age.

Santos et al.[12] reported that the presence of other comorbid food allergies increased the risk of persistence. In parallel with this study, comorbid food allergies in our study increased the risk of persistence. Thus, based on the literature and the findings of the current study, the presence of multiple food allergies appears to increase the risk of persistence.

The present study has a few limitations that could influence the results of the study. First, as this was a retrospective study, patients who had missing file reports were not included in the study. Second, the majority of patients with CMPA-related proctocolitis are referred to gastroenterology clinics. Thus, most patients in the present study had IgE-mediated reactions to CMPA. Third, the follow-up periods of the patients were short.

Conclusion

Tolerance to CMPA, a food allergy, can develop over time. Thus, CMPA has a good prognosis. However, CMPA due to an IgE-mediated allergy, the presence of respiratory system symptoms (ie, tachypnea), or the presence of a comorbid food allergy have negative effects on tolerance development. In contrast, CMPA due to a non–IgE-mediated allergy or CMPA that is associated with gastrointestinal discomfort have positive effects on the development of tolerance.

References

1. Host A. Frequency of cow's milk allergy in childhood. *Ann Allergy Asthma Immunol*. 2002;89 (6 Suppl 1):33–37.
2. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. *J Allergy Clin Immunol*. 2010;126:1105–1118.
3. ESPGHAN Committee on Nutrition, Agostoni C, Braegger C, Decsi T, et al. Breastfeeding: a commentary by the ESPGHAN committee of nutrition. *J Pediatr Gastroenterol Nutr*. 2009;49:112–125.
4. Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol*. 2007;120:638–646.
5. Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol*. 2011;127:594–602.
6. Host A, Halken S, Jacobsen HP, et al. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. *Pediatr Allergy Immunol*. 2002;13(Suppl 15):23–28.
7. Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr*. 1989;115:23–27.
8. Host A. Cow's milk protein allergy and intolerance in infancy. *Pediatr Allergy Immunol*. 1994;5:5–36.
9. Saarinen KM, Pelkonen AS, Mäkelä 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. Vanto T, Helppila S, Juntunen-Backman K, et al. Prediction of the development of tolerance to milk in children with cow's milk hypersensitivity. *J Pediatr*. 2004;144:218–222.
11. Ahrens B, Lopes de Oliveira LC, Grabenhenrich L, et al. Individual cow's milk allergens as prognostic markers for tolerance development? *Clin Exp Allergy*. 2012;42:1630–1637.
12. Santos A, Dias A, Pinheiro JA. Predictive factors for the persistence of cow's milk allergy. *Pediatr Allergy Immunol*. 2010;21:1127–1134.
13. Shek LP, Soderstrom L, Ahlstedt S, et al. Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy. *J Allergy Clin Immunol*. 2004;114: 387–391.
14. Koike Y, Sato S, Yanagida N, et al. Predictors of persistent milk allergy in children: a retrospective cohort study. *Int Arch Allergy Immunol*. 2018;175: 177–180.