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Original Research

Effects of Cow's Milk Components, Goat's Milk and Sheep's Milk Sensitivities on Clinical Findings, and Tolerance Development in Cow's Milk Allergy

Nursen Cigerci Gunaydin,[1] Ezgi Ulusoy Severcan,[2] Sanem Eren Akarcan,[3] Cem Murat Bal,[3] Figen Gulen,[3] Remziye Tanac,[3] Esen Demir[3]

[1]Department of Pediatrics, Division of Pediatric Allergy and Immunology, Namık Kemal University, Faculty of Medicine, Tekirdag, Turkey
[2]Department of Pediatric Immunology and Allergy, University of Health Sciences Turkey, Dr. Sami Ulus Maternity and Children Research and Training Hospital, Ankara,Turkey
[3]Department of Pediatrics, Division of Pediatric Allergy and Immunology, Ege University Faculty of Medicine, Izmir, Turkey

Abstract

Objective: Cow's milk (CM) contains some proteins capable of causing an allergic reaction in a sensitized individual and one of the most common causes of food allergy in childhood. Most of the patients will develop tolerance by the age of 3. In this study, we aimed to evaluate sensitivity to CM allergen components as well as goat's milk (GM) and sheep's milk cross reactions in cow's milk allergic (CMA) patients and to figure out the risk factors for tolerance non-development.

Methods: This is a retrospective cross-sectional study including 66 patients for IgE-mediated CMA with mean age of 38 months. We evaluated the patients in two groups: Group 1 (*n*=50): Patients who have no tolerance in oral food challenge test; Group 2 (*n*= 16): Patients who were found tolerant to CM after elimination diet. Cow's milk-spesific IgE(sIgE), α-lactalbumin(ALA)-sIgE, β-Lactoglobulin(BLG)-sIgE, casein-sIgE, goat's milk-sIgE, sheep's milk-sIgE, skin prick tests(SPTs) with CM and GM, eosinophils in peripheral blood were all compared between two groups.

Results: In the whole group, goat's milk-sIgE and sheep's milk-sIgE were positive in 84.8% and ALA-sIgE, BLG-sIgE, casein-sIgE were positive in 69.7%, 62.7%, 77.3% of the patients, respectively. Two groups were similar in terms of age at onset and diagnosis, gender, median elimination period, total IgE levels, cow's milk-sIgE and eosinophilia (p>0.05). Mean wheal diameters of CM and GM in SPT (p<0.001), goat's milk-sIgE (p=0.03), sheep's milk-sIgE (p=0.01) were significantly higher in Group 1. Cow's milk-sIgE showed a positive correlation with total IgE (p=0.001), eosinophilia percentage (p=0.04), CM wheal diameter in SPT (p=0.001), casein-sIgE (p<0.001), goat's milk-sIgE (p<0.001), sheep's milk-sIgE (p<0.001) in Group 1. Patients with respiratory symptoms and history of anaphylaxis had higher cow's milk-SPT, cow's milk-sIgE, casein-sIgE, goat's milk-sIgE, sheep's milk-sIgE levels(p<0.05). Gastrointestinal and skin symptoms showed no relation with laboratory findings. Any patient with a history of anaphylaxis did not develop tolerance.

Conclusions: As with cow's milk-sIgE levels and high induration diameters in SPT; high casein-sIgE, sheep's milk-sIgE and goat's milk-sIgE levels are also risk factors for persistence of CMA. Anaphylaxis, as a first reaction, may also be a risk factor. High cow's milk-sIgE, casein-sIgE, sheep's milk-sIgE, goat's milk-sIgE levels are associated with respiratory symptoms.

Keywords: Caseins, children; cow's milk allergy; goat's milk; sheep's milk; whey proteins.

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Address for correspondence: Nursen Cigerci Gunaydin, MD. Department of Pediatrics, Division of Pediatric Allergy and Immunology, Namık Kemal University Faculty of Medicine, Namık Kemal, Kampüs Street No:1, Suleymanpasa, Tekirdag, Turkey
Phone: +90 282 250 00 00 **E-mail:** drnursen@hotmail.com

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Introduction

Cow's milk allergy (CMA) is the most common food allergy seen in children with a prevalence of 2–5% worldwide.[1-3] Most of the children with CMA become tolerant to milk at 3 years.[4,5] In IgE-mediated CMA, symptoms appear within minutes or hours after consuming milk or milk products. Skin manifestations (urticaria/angioedema), respiratory symptoms (sneezing, wheezing, and dyspnea), gastrointestinal symptoms (nausea, vomiting, and abdominal pain), or anaphylaxis may occur.[6]

Clinical history, skin prick test (SPT), cow's milk (CM)-specific IgE levels, and oral food challenge (OFC) test are the basis of diagnosis. SPTs and specific IgE (sIgE) levels demonstrate sensitization, but food challenge test is the gold standard for the diagnosis of clinical allergy. There is not a definitive treatment for CMA.[3] Management involves rescue medication in the event of accidental reactions and avoidance of CM.[7]

Cow's milk contains more than 40 different proteins, all of which may act as antigens. The main allergens are caseins and whey proteins, α-lactalbumin (ALA) and β-lactoglobulin (BLG).[8-10] In CMA, all IgE molecules do not have equal level of pathogenicity, persistent allergy may relate to some IgE types specific to different epitopes.[11,12] There can be also reactions with phylogenetically related animal milks such as water buffalo, sheep, goat, and horse because of similar milk protein expression.[6] The casein plays the main role regarding the cross-reactivity among bovine's milk and other mammalian milks.[13] Clinical cross-reactivity with goat's milk (GM) is 90–92% and sheep's milk (SM) is quite high.[14-17]

Various levels of component sensitivity were reported in different studies. In this study, we aimed to investigate sensitization patterns against cow's milk allergen components as well as goat's milk (GM) and sheep's milk (SM) sensitivity in CM allergic patients and to figure out the risk factors for tolerance non development.

Material and Methods

This is a retrospective cross-sectional study, including 66 patients who were followed up in the pediatric allergy clinic for IgE mediated cow's milk allergy with a mean age of 38 months. The patients who had a sudden allergic reaction associated with intake of CM were investigated for IgE-associated CMA with SPT and cow's milk-sIgE measurements. Patients who had a positive OFC result or a clear-cut history of anaphylaxis after milk ingestion were diagnosed as IgE-mediated CMA according to guidelines.[18]

The CMA diagnosis was first proven by open OFC test with formula (in children under 1 year old) or CM (in children older than 1 year). Open OFC tests were repeated at 6-month or 1-year intervals to evaluate the development of tolerance. If the symptoms were resolved with CM elimination diet and OFC test was negative, it was considered as tolerance development to CM and patients started to consume CM.

The patients with IgE-mediated cow's milk allergy were evaluated in two groups according to the development of tolerance. Group 1 (n=50): Patients who were found not tolerant to cow's milk with OFC test and still following an elimination diet. Group 2 (tolerant- group) (n=16): Patients who were found tolerant to CM with OFC test after elimination diet. The median elimination diet period was 24 (6-130) months in patients. Total IgE, CM-sIgE, ALA-sIgE, BLG-sIgE, casein-sIgE, goat's milk-sIgE and sheep's milk-sIgE, skin prick tests with CM and GM, percentage of eosinophils in peripheral blood were all compared between two groups. To identify accompanying egg allergy, SPTs and sIgE levels with egg were performed.

Skin Prick Test

SPTs were performed to all patients with fresh food (one drop of each fresh milk containing 3.5% fat) and commercial extracts (ALK-Abello A/S, Horsholm, Denmark standard prick test solutions for cow's milk and hen's egg). Single-peak lancets (1 mm diameter) (stallerpoint, Stallergenes, SA, laboratories) were used to prick the skin. Histamine (10 mg/ml) was used as positive control and NaCl (0.9%) was used for negative control. A wheal size ≥ 3 mm larger than the negative control was accepted as positive.

Specific IgE Measurement

The total serum IgE and sIgE to CM proteins (α-lactalbumin, β-lactoglobulin, casein), whole cow's milk, goat's milk and sheep's milk were determinated using the CAP system-FEIA (Pharmacia Upjhon). Specific IgE titres were quantified in protein units designated as kilo units of antibody per litre (kU/L). sIgE ≥ 0.35 was considered positive.

OFC Test

OFC tests were started using 0.1 mL diluted pasteurized CM with 3.3% protein content (1:10, milk:water) and were continued with increasing amounts of undiluted milk every 15–30 min until the amount of 200 mL CM (6540 mg milk protein) was taken or until a reaction was noted. Oral challenge results were considered positive when objective symptoms occurred. Urticaria, angioedema, airway obstruction signs (e.g., dyspnea, rales, and rhonchi), vomiting, and anaphylaxis were evaluated as the objective reactions.[18,19] Sensitive patients with no reactions in OFC were accepted as tolerant.

Statistical Analysis

In the study, statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA), version 23.0 software. Descriptive statistics were presented with mean, standard deviation, median, minimum and maximum values, frequencies, and percentages. Whether the distribution of each variable in the dataset fits the normal distribution was tested and variables that were not suitable for normal distribution were evaluated by non-parametric tests. A Chi-square test was used in the analysis of categorical data. Mann–Whitney U-test was used in binary independent group comparison. The Pearson correlation analysis was performed to assess the correlation between the scale scores. The results were evaluated at a significance level of $p<0.05$.

Demographic and clinical characteristics of the patients and laboratory results were recorded to questionnaire forms for every patient. The study was approved by the local ethics committee (IRB No. 20-5.1T/59) and informed consent was obtained from all parents/guardians.

The sample size of this research was calculated with G * Power V3.1.9.7 software. The effect size was calculated as 0.901 based on average casein sIgE in patients with and without tolerance due to the literature. The minimum sample size was calculated as 32 (16 people in both groups) with d=0.901 sampling error at 95% (α=0.05) confidence interval limits for a power of 0.80.

All non tolerant patients were included in the study to evaluate the relationship between clinical and laboratory findings of these patients (n=50).

Results

Sixty-six patients with immunoglobulin-E-mediated CMA, 43 (65.1%) of whom were female were evaluated in this study. Most patients presented first symptoms within 6 months of age and average age of diagnosis was 7.8±4.7 months. Mean age of onset and diagnosis was 6.7±2.8 (2–18) and 7.8±4.7 (2–24) months, respectively. Mean age of the patients at study time was 38±7.1 (32–164) months.

More than half of the patients had a family history of atopy (54.5%). First reactions developed after consuming yogurt or formula, mostly. The symptoms were consisted of skin reactions (including urticarial and/or angioedema) (86.9%, *n*=57), respiratory distress (including cough, bronchospasm, or wheezing) (23%, *n*=15), gastrointestinal symptoms (23%, *n*=15), and anaphylaxis (7.5%, *n*=5). There was hen egg sensitivity in seven patients. Two of them who were in elimination group had hen egg allergy. 73% (n:48) of the patients had a reaction history after consumption of goat's or sheep's milk.

Tolerance to CM developed in 24.2% (*n*=16) of all patients (patients in Group 2). The median elimination diet period was 24 (6–130) months in Group 1 and the median elimination period before tolerance development was 23 (6–36) months in Group 2.

In Group 1, the median cumulative provocative dosage of OFC test was 6±7.5 mL (180 mg milk protein). The provocation reactions consisted of urticaria (70.8%), respiratory distress findings (including bronchospasm, wheezing, and/or sibilant rhonchi) (24%), angioedema (12%), and vomiting (2.3%).

In all patients, goat's milk-sIgE and sheep's milk-sIgE were both 84.8% positive and percentage of positivity of ALA-sIgE, BLG-sIgE, casein-sIgE were 69.7%, 62.7%, 77.3%, respectively.

In the whole group, goat's milk-sIgE and sheep's milk-sIgE were both positive in 84.8% and ALA-sIgE, BLG-sIgE, casein-sIgE were positive in respectively 69.7%, 62.7%, 77.3% of the patients.

Table 1 shows median age of onset, gender, and median levels of sIgE for CM, CM components (CAS, ALA, and BLG), GM, and SM, and median diameters in SPT for CM and GM in both groups.

Two groups were similar in terms of gender, age at onset and diagnosis, levels of total IgE, CM-sIgE, ALA-sIgE, BLG-sIgE and percentage of eosinophilia %. The mean wheal diameters of CM and GM in SPTs, casein-sIgE, goat's milk-sIgE, sheep's milk-sIgE were significantly higher in Group 1 (Table 1 and Figs. 1-3).

In both Groups 1 and 2, casein-sIgE was positively correlated with ALA-sIgE ($p<0.001$, $p=0.003$, respectively), goat's milk-sIgE ($p<0.001$, $p<0.001$, respectively), sheep's milk-sIgE ($p<0.001$, $p<0.001$, respectively); whereas not correlated with BLG-sIgE ($p=0.12$, $p=0.12$, respectively) (data not shown).

Patients with respiratory symptoms and history of anaphylaxis had higher CM-SPT, CM-sIgE, casein-sIgE, goat's milk-sIgE and sheep's milk-sIgE levels (Table 2).

In Group 1, cow's milk-sIgE was positively correlated with total IgE, eosinophils %, CM wheal diameter in SPT, casein-sIgE, goat's milk-sIgE, sheep's milk-sIgE. There was no correlation between provocative dosage in OFC test and laboratory tests in this group (Table 3). In Group 2, cow's milk-sIgE was correlated with all laboratory parameters except total IgE (Table 3).

Table 1. Demographic and laboratory features of the patients according to the groups

Laboratory features	Group 1 (*n*=50)	Group 2 (*n*=16)	*P*
Median age of onset (months)	7.7 (2–24)	6.7 (2–18)	0.81
Gender (female)	68% (*n*=34)	62.5% (*n*=10)	0.29
Total IgE (IU/ml)	341±200	243±219	0.41
Eosinophil %	4.2±3	4.7±3.8	0.6
Cow's milk-SPT (mm)	10.6±6.4	3±4.2	**<0.001**
Goat's milk-SPT (mm)	9.6±6.9	2.5±2	**<0.001**
CM-sIgE (kUA/l) (median)	14.6 (1–162)	4 (1.2–45)	0.06
ALA-sIgE (kUA/l) (median)	4.4 (0.7–100)	0.32 (0.8–34)	0.08
BLG-sIgE (kUA/l) (median)	3.27 (0.5–100)	0.25 (0.4–24)	0.06
Casein-sIgE (kUA/l) (median)	9.5 (0.9–136)	0.32 (0–54)	**<0.001**
Goat's milk sIgE (kUA/l) (median)	9.2 (0–124)	0.6 (0–57)	**0.003**
Sheep's milk-sIgE (kUA/l) (median)	11 (0–125)	0.64 (0-84)	**0.01**

CM: Cow's milk, A-LA: α-Lactalbumin; BLG: β-Lactoglobulin; CAS: Casein; GM: Goat's milk; SM: Sheep's milk; SPT: Skin prick test.

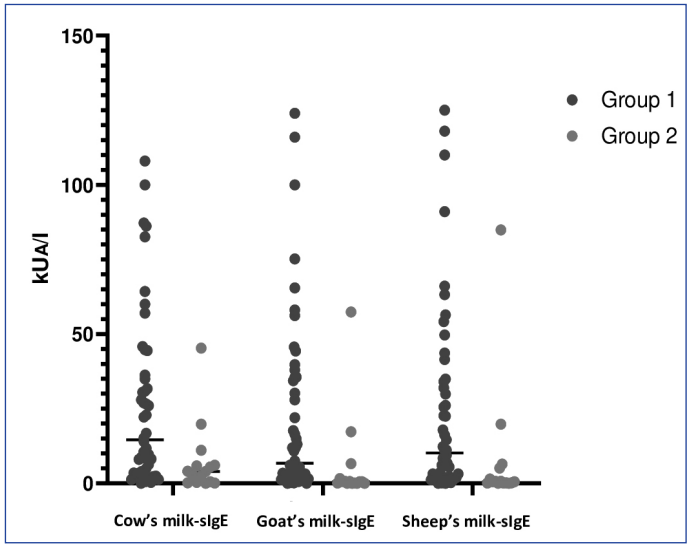

Figure 1. The CM-sIgE, GM-sIgE, and SM-sIgE measurements of the patients according to the groups. CM: Cow's milk, GM: Goat's milk, SM: Sheep's milk.

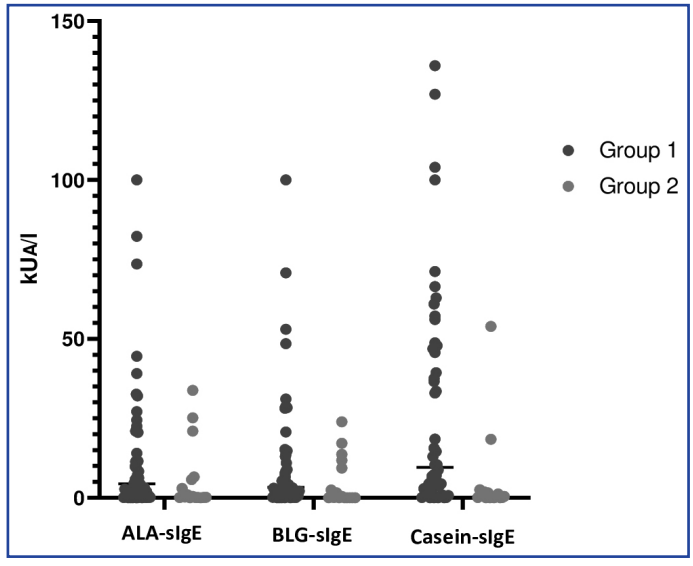

Figure 2. The ALA-sIgE, BLG-sIgE, and CAS-sIgE measurements of the patients according to the groups. ALA: α-Lactalbumin; BLG: β-Lactoglobulin; CAS: Casein.

Anaphylaxis (n=5) were seen mostly with higher cow's milk-SPT (14.5±10 [4-35] mm; 10±5.7 [0-30] mm, p=0.04), median cow's milk-sIgE (44.8 [0-100] kUA/l; 11.8 [0-86] kUA/l, p=0.02), median casein-sIgE (37.4 [0-136]; 8.7 [0-100] kUA/l, p=0.02), median goat's milk-sIgE (35.5 [0-100] kUA/l; 6.7 [0-124] kUA/l, p=0.03), median sheep's milk-sIgE (29.9 [0-125] kUA/l; 8.9 [0-118] kUA/l, p=0.03), respectively.

Discussion

CMA is the most common food allergy in childhood.[20] In this study, we evaluated sensitization patterns against cow's and milk allergen components as well as GM and SM sensitivity in CMA and to investigate these factors to distinguish children with persistent CMA from children developing tolerance.

Component diagnostic testing may provide more accurate assessments of clinical reactivity to food allergens.[21] Docena *et al*.[22] identified casein as the major allergenic protein of CM. According to their study, all patients' sIgE levels were positive for milk and casein, and 17.5% for BLG and 5% for ALA. World allergy organization guidelines 2010 reported alpha-lactalbumin role in milk allergy according

to data studies as 0–80%.[6] Beta-lactoglobulin, which is the most abundant CM whey protein, was reported to affect 13–76% of patients. In 2012, Chen *et al*.[23] reported a different distribution of CM protein sensitization of Taiwanese patients as the sensitization rate to ALA-sIgE was 60%, followed by BLG (46.8%) and casein (40.5%). Jessadapakorn *et al*. study, the sensitization rate to BLG and casein was 91.7%, followed by ALA (66.7%) for CMA.[24]

In this study, it was remarkable the positivity rate of milk components sIgE in patients with no tolerance (Group 1), all of three components sIgE percentages were found high as ALA-sIgE 74%, bLG-sIgE 82%, and casein-sIgE 86%.

This study has shown that the patients in CMA tend to consume other mammals milk (73% of the patients). For cross reactivity we looked to goat's milk-sIgE and sheep's milk-sIgE levels, in 84.8% of the patients both were found elevated as other studies in different societies.

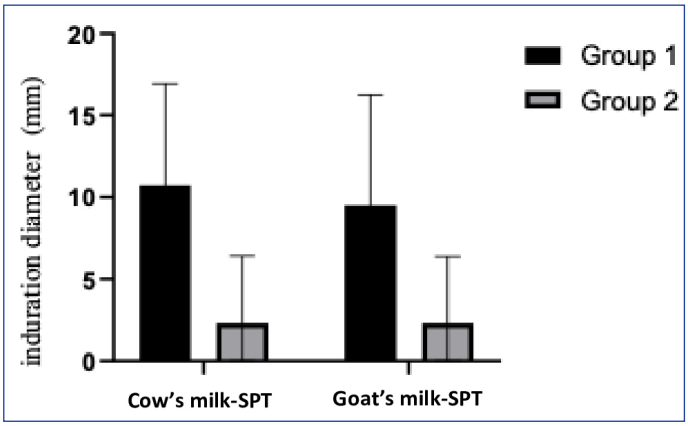

Figure 3. The wheal diameter of CM and GM in SPT of the patients according to the groups. CM: Cow's milk, GM: Goat's milk, SPT: Skin prick test.

The cow's milk proteins and biological properties similar to the milk of other mammals.[17] In literature, especially alpha casein in cow's, goat's and sheep's milk is highly cross reactive.[25,26]

To date guidelines recommends highly hydrolysed or amino acid formula instead of cow's milk to CMA patients younger than 2 years old as an alternative therapy but not other mammalien milks.[6]

In Høst and Halken study, the overall prognosis of CMA was good with a total recovery of 87% at 3 years.[27] Studies have reported risk factors for the development of tolerance. In some studies, high wheal diameter of CM in SPT were and high CM-sIgE levels also reported as risk factor for tolerance.[28-30] Moreover, high casein levels were also found related with the persistence of CMA.[11,12] In Sicherer *et al*.[31] has defined high casein and cow's milk sIgE levels as risk factors for persistent CMA.

In our study similar to the literature cow's milk-sIgE and casein-sIgE levels were found high in patients with no tolerance to CM. Beyond these studies we also found an association with elevated GM and sheep's milk-sIgE levels with persistance of CMA. Besides, this study showed that goat's milk wheal diameter in SPT is to be a risk factor in CMA. The low levels of goat's milk-sIgE and sheep's milk-sIgE in tolerance group is remarkable.

Table 2. Laboratory parameters according to respiratory symptoms in Group 1

Laboratory parameters	Respiratory findings		*P*
	Yes (*n*=12)	No (*n*=38)	
Cow's milk-SPT (mm)	12±10	7±5.9	**0.04**
Goat's milk-SPT (mm)	10.6±8.3	7±6.7	0.12
Cow's milk-sIgE (kUA/l) (median)	26.4 (0.35–162)	17.6 (0–100)	**0.03**
ALA-sIgE (kUA/l) (median)	5.8 (0–82)	4.4 (0–100)	0.15
BLG-sIgE (kUA/l) (median)	7.1 (0–53)	3.3 (0–100)	0.19
Casein-sIgE (kUA/l) (median)	33 (0.3–136)	13±17 (0–71)	**0.02**
Goat's milk-sIgE (kUA/l) (median)	10.3 (0–124)	7.3 (0–75)	**0.04**
Sheep's milk-sIgE (kUA/l) (median)	24 (0–125)	11 (0–91)	**0.03**
Eosinophils%	4.7±3	3.4±2.8	**0.02**

ALA: α-Lactalbumin; BLG: β-Lactoglobulin; SPT: Skin prick test.

Table 3. Evaluation of the correlation between laboratory findings and CM-sIgE in Groups and provocative dosage of OFC tests in Group 1

Groups	Total IgE	Eosinophil %	CM-SPT	Goat's milk-SPT	ALA-sIgE	BLG-sIgE	Casein-sIgE	Goat's milk-sIgE	Sheep's mik-sIgE
Group I									
CM-sIgE	r=0.473	r=0.312	r=0.488	r=0.289	r=0.234	r=0.452	r=0.590	r=.529	r=0.529
	***p*=0.001**	***p*=0.045**	***p*=0.001**	*p*=0.07	*p*=0.11	*p*=0.11	***p*<0.001**	***p*<0.001**	***p*<0.001**
Provacative dosage of OFC tests	r=0.218	r=0.009	r=0.028	r=0.142	r=–0.034	r=-0.07	r=–0.23	r=–0.019	r=–0.235
	p=0.55	*p*=0.05	*p*=0.85	*p*=0.39	*p*=0.95	*p*=0.6	*p*=0.12	*p*=0.2	*p*=0.11
Group II									
CM-sIgE	r=0.302	r=0.768	r=0.788	r=0.651	r=0.808	r=0.608	r=0.931	r=0.935	r=0.937
	p=0.25	***p*<0.001**	***p*<0.001**	***p*=0.006**	***p*<0.001**	***p*=0.013**	***p*<0.001**	***p*<0.001**	***p*<0.001**

OFC: Oral food challenge; CM: Cow's milk; ALA: α-Lactalbumin; BLG: β-Lactoglobulin; CAS: Casein; GM: Goat's milk; SM: Sheep's milk; SPT: Skin prick test.

Ahrens *et al*.[32] reported that children became tolerant earlier if their sIgE levels against the two whey proteins from CM; ALA-sIgE and BLG-sIgE and against two of the four casein fractions αs1 and κ-casein- sIgE were low. In our study, levels of ALA-sIgE and BLG-sIgE were lower in elimination group but it wasn't statistically significant. We didn't find any relationship with tolerance and total IgE levels, gender, percentage of eosinophils, age of onset and diagnosis.

In Petersen et al.[33] study, a correlation between sIgE level to cow's milk and casein and the severity of the allergic reaction by food challenges was found. In our study, we showed that respiratory symptoms and anaphylaxis were associated with high CM-sIgE levels. Besides, casein-sIgE, goat's milk-sIgE, sheep's milk-sIgE levels were also elevated in patients with respiratory symptoms. But, we didn't find any relation between milk component levels and different symptoms. None of the patients developed a tolerance for CM had anaphylaxis as reaction whereas 5 allergic patients first reaction was anaphylaxis which can be also considered as a risk factor for tolerance.

Study Limitations

There are several limitations to this study. The diagnosis of CMA was not based on double-blind, placebo-controlled food challenges. However, only objective findings in open OFC test or history of anaphylaxis after ingestion of CM were considered significant for diagnosis. There is no doubt about the diagnosis of CMA in children. Because of a reactions was reported by their families due to the consumption of other mammalian milk on 73% of these patients, and high sIgE positivity and measurements were detected in all, we didn't perform OFC tests with goat's and sheep's milk.

Conclusions

As with CM-sIgE levels and high wheal diameters in SPT, high casein-sIgE, sheep's milk-sIgE, goat's milk-sIgE levels are also risk factors for persistence of CMA. Anaphylaxis, as a first reaction, may also be a risk factor. High cow's milk-sIgE levels, casein-sIgE, sheep's milk-sIgE, goat's milk-sIgE are associated with respiratory symptoms. It should be considered that sensitivity to GM and SM may also be high, especially in patients with high cow's milk-sIgE, casein-sIgE or CM induration diameters in SPT.

Disclosures

Ethics Committee Approval: Ethics committee approval of the study was obtained from the ethics committee of Ege University with the date and number of 2020-IRB No.20-5.1T/59.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – N.C.G., E.D.; Design – N.C.G., E.U.S., E.D.; Supervision – F.G., R.T.; Materials – N.C.G., E.U.S., S.E.A., F.G.; Data collection &/or processing – N.C.G., S.E.A., C.M.B.; Analysis and/or interpretation – N.C.G., E.U.S., E.D.; Literature search – C.M.B., S.E.A.; Writing – N.C.G., E.U.S.; Critical review – R.T., E.D.

References

1. Ruszczyński M, Horvath A, Dziechciarz P, Szajewska H. Cow's milk allergy guidelines: a quality appraisal with the AGREE II instrument. Clin Exp Allergy 2016;46:1236–41. [CrossRef]
2. Patel BY, Volcheck GW. Food Allergy: Common Causes, Diagnosis, and Treatment. Mayo Clin Proc 2015;90:1411–9. [CrossRef]
3. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: food allergy. J Allergy Clin Immunol 2012;129:906–20. [CrossRef]
4. Sánchez-García S, Cipriani F, Ricci G. Food Allergy in childhood: phenotypes, prevention and treatment. Pediatr Allergy Immunol 2015;26:711–20. [CrossRef]

5. 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;116:869–75. [CrossRef]
6. Fiocchi A, Brozek J, Schünemann H, Bahna SL, von Berg A, Beyer K, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. World Allergy Organ J 2010;3:57–161. [CrossRef]
7. Carrard A, Rizzuti D, Sokollik C. Update on food allergy. Allergy 2015;70:1511–20. [CrossRef]
8. Wal JM. Cow's milk proteins/allergens. Ann Allergy Asthma Immunol 2002;89:3–10. [CrossRef]
9. Restani P, Gaiaschi A, Plebani A, Beretta B, Cavagni G, Fiocchi A, et al. Cross-reactivity between milk proteins from different animal species. Clin Exp Allergy 1999;29:997–1004. [CrossRef]
10. Shokouhi Shoormasti R, Fazlollahi MR, Barzegar S, Teymourpour P, Yazdanyar Z, Lebaschi Z, et al. The most common cow's milk allergenic proteins with respect to allergic symptoms in Iranian patients. Iran J Allergy Asthma Immunol 2016;15:161–5.
11. Chatchatee P, Järvinen KM, Bardina L, Vila L, Beyer K, Sampson HA. Identification of IgE and IgG binding epitopes on beta- and kappa-casein in cow's milk allergic patients. Clin Exp Allergy 2001;31:1256–62. [CrossRef]
12. Vila L, Beyer K, Järvinen KM, Chatchatee P, Bardina L, Sampson HA. Role of conformational and linear epitopes in the achievement of tolerance in cow's milk allergy. Clin Exp Allergy 2001;31:1599–606. [CrossRef]
13. Järvinen KM, Chatchatee P. Mammalian milk allergy: clinical suspicion, cross-reactivities and diagnosis. Curr Opin Allergy Clin Immunol 2009;9:251–8. [CrossRef]
14. Sicherer SH. Clinical implications of cross-reactive food allergens. J Allergy Clin Immunol 2001;108:881–90. [CrossRef]
15. Turnbull JL, Adams HN, Gorard DA. Review article: the diagnosis and management of food allergy and food intolerances. Aliment Pharmacol Ther 2015;41:3–25. [CrossRef]
16. Restani P, Beretta B, Fiocchi A, Ballabio C, Galli CL. Cross-reactivity between mammalian proteins. Ann Allergy Asthma Immunol. 2002;89:11–5. [CrossRef]
17. Martorell-Aragonés A, Echeverría-Zudaire L, Alonso-Lebrero E, Boné-Calvo J, Martín-Muñoz MF, Nevot-Falcó S, et al; Food allergy committee of SEICAP (Spanish Society of Pediatric Allergy, Asthma and Clinical Immunology). Position document: IgE-mediated cow's milk allergy. Allergol Immunopathol (Madr) 2015;43:507–26. [CrossRef]
18. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, et al; European Academy of Allergology and Clinical Immunology. Standardization of food challenges in patients with immediate reactions to foods--position paper from the European Academy of Allergology and Clinical Immunology. Allergy 2004;59:690–7. [CrossRef]
19. Vandenplas Y, Koletzko S, Isolauri E, Hill D, Oranje AP, Brueton M, et al. Guidelines for the diagnosis and management of cow's milk protein allergy in infants. Arch Dis Child 2007;92:902–8. [CrossRef]
20. Can C, Altinel N, Bülbül L, Civan HA, Hatipoğlu S. Clinical and laboratory characteristics of patients with food allergy: single-center experience. Sisli Etfal Hastan Tip Bul 2019;53:296–9. [CrossRef]
21. Wang J. Utility of component diagnostic testing in guiding oral food challenges to milk and egg. Allergy Asthma Proc 2016;37:439–42. [CrossRef]
22. 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. [CrossRef]
23. Chen FM, Lee JH, Yang YH, Lin YT, Wang LC, Yu HH, et al. Analysis of α-lactalbumin-, β-lactoglobulin-, and casein-specific IgE among children with atopic diseases in a tertiary medical center in Northern Taiwan. J Microbiol Immunol Infect 2014;47:130–6. [CrossRef]
24. Jessadapakorn W, Sangsupawanich P, Wootipoom N, Suddeaugrai O, Yuenyongviwat A. Component-resolved diagnostics in Thai children with cow's milk and egg allergy. Asian Pac J Allergy Immunol 2017;35:179–85.
25. Spuergin P, Walter M, Schiltz E, Deichmann K, Forster J, Mueller H. Allergenicity of alpha-caseins from cow, sheep, and goat. Allergy 1997;52:293–8. [CrossRef]
26. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol 2014;134:1016–25. [CrossRef]
27. 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. [CrossRef]
28. Berin MC. Mechanisms that define transient versus persistent food allergy. J Allergy Clin Immunol 2019;143:453–7. [CrossRef]
29. Wood RA, Sicherer SH, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of milk allergy in an observational cohort. J Allergy Clin Immunol 2013;131:805–12. [CrossRef]
30. Lifschitz C, Szajewska H. Cow's milk allergy: evidence-based diagnosis and management for the practitioner. Eur J Pediatr 2015;174:141–50. [CrossRef]
31. 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. [CrossRef]
32. Ahrens B, Lopes de Oliveira LC, Grabenhenrich L, Schulz G, Niggemann B, Wahn U, et al. Individual cow's milk allergens as prognostic markers for tolerance development? Clin Exp Allergy 2012;42:1630–7. [CrossRef]
33. Petersen TH, Mortz CG, Bindslev-Jensen C, Eller E. Cow's milk allergic children-Can component-resolved diagnostics predict duration and severity? Pediatr Allergy Immunol 2018;29:194–9. [CrossRef]