

The significance of allergic contact urticaria to milk in children with cow's milk allergy

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Abstract

Background: Cow's milk allergy (CMA) is the most common food allergy in infancy. Food allergy is generally triggered through ingestion, but can also be triggered through skin contact. We investigated the incidence and the clinical significance of cow's milk protein (CMP)-induced contact urticaria in individuals with CMA with and without atopic dermatitis (AD).

Methods: A total of 157 children of whom 133 were diagnosed with CMA were participated. The study was based on observational data gathered in the course of patient care, including a skin prick test and a 'finger test', in which cow's milk is applied on the cheek by a physician's finger to detect contact urticaria.

Results: Eighty nine of 133 patients (66.9%) had IgE-mediated CMA. Forty of these 89 (44.9%) tested positive in the finger test. Family atopy was higher in those with positive contact urticaria [21/40 (52.5%) vs. 14/49 (28.5%), $p = 0.029$]. Patients with positive vs. negative CMP contact urticaria had higher incidence of multiple food allergies [20 of 40 (50%) vs. 7/49 (14.3%), $p < 0.004$]. IgE-mediated CMA patients with AD had statistically higher CMP allergic contact urticaria compared to patients without AD [71% (15/21) vs. 37% (25/68), $p = 0.0064$]. Children with non-IgE milk allergy and healthy control group did not have contact urticaria to CMP.

Conclusion: CMP contact urticaria exists only in patients with IgE-mediated CMA. A 'finger test' to CMP should be part of the evaluation of CMA patients, and positivity suggests the potential for multiple food allergies, especially to sesame and egg.

Cow's milk allergy (CMA) is the most common food allergy in infants and young children, affecting 2–3% of the general population (1). In a large, prospective population-based study recently conducted in Israel, the cumulative incidence of IgE-mediated CMA was 0.5%; the incidence of non-IgE-mediated adverse effects was also 0.5% (2). The milk allergy rate was found to exceed the rate of allergies to egg, sesame seeds, peanuts and tree nuts (3). Risk factors for food allergy include male gender, genetics and atopy diathesis (atopic dermatitis (AD), asthma and allergic rhinitis) (4). Food allergy evaluations require a careful clinical history, along with a skin prick test (SPT) and/or specific IgE to food allergens. However, the double-blind oral food challenge test is the gold standard.

Food allergies are generally triggered through ingestion. However, skin contact and food inhalation can also trigger allergic reactions (5). IgE-mediated contact urticaria syndrome

(CUS) is one of the manifestations of allergy in childhood AD. Allergens such as foods and animal products can penetrate the skin, causing urticarial reactions in sensitized individuals (6).

Parents of children allergic to cow's milk protein (CMP) who attend our allergy clinic for evaluation frequently report redness or urticaria appearing on the skin of the face after it accidentally comes into contact with cow's milk. These symptoms suggest a food-induced immediate contact reaction, which may be immune-mediated or a result of skin irritation.

In the past, allergic contact urticaria to CMP and other food allergens (egg and nuts) was investigated only in individuals with AD (6, 7). The positive skin reaction was explained by the penetration of allergens through the injured skin.

Our study was designed to test this phenomenon mainly in none AD individuals with CMA. We exposed CMA patients

with and without AD to contact with cow's milk with the aim of inducing the urticarial reaction. We investigated the incidence and the clinical significance of cow's milk-induced contact urticaria in these two groups of allergic patients.

Patients and methods

Patients

The study group consisted of children under the age of 18 yr treated at our outpatient allergy clinic at Bnai Zion Medical Center, Haifa, Israel, for IgE and non-IgE CMA from December 2012 through March 2014. The diagnosis of IgE-mediated CMA was made on the basis of a positive SPT to CMP and by convincing documented compatible clinical history or oral cow's milk challenge. During follow-up, data were collected on additional food allergy reactions, and in cases of suspected IgE-mediated food allergy, a SPT was performed to confirm diagnosis. In selected cases, a food challenge test was conducted. Non-IgE cow's milk allergic patients were diagnosed based on clinical history, a negative SPT and a positive oral challenge test.

The patients' files were reviewed for age, symptoms and signs of the allergic reaction, diameter of SPT, additional allergic diseases (allergic rhinitis, asthma, AD, other food allergies) and family history of atopic diseases.

The full study population comprised 133 patients, including 89 diagnosed with IgE-mediated CMA and 44 with non-IgE-mediated CMA. Twenty-four healthy non-allergic children who were not suffering from AD or any other skin disease were enrolled as a control group. The 89 patients with IgE-mediated CMA included 43 females (48.3%) and 46 males (51.7%), mean age 25.6 ± 37.0 months.

Fifty-six of them (56/89, 62.9%) were under the age of 2 yr (11 ± 4.6 months, mean $\pm$ s.d.) with a previous clinical reaction to cow milk within a mean of 5.1 ± 3.9 months and a cow milk SPTs mean wheal of 4.4 ± 3.9 mm. Thirty-two patients (37.1%) were older than 2 yr (73.9 ± 48.9 months) with a previous reaction to cow milk protein within a mean of 13.8 ± 9.9 months and had a mean wheal of 7.5 ± 2.9 in SPTs. In 12 cases of uncertainty (12/89, 13.4%), the diagnosis of CMA was verified by positive cow milk protein challenge test.

The 44 patients with non-IgE CMA were diagnosed with food protein-induced enterocolitis syndrome (FPIES), food protein-induced enteropathy, or proctocolitis. They included 25 females (56.8%) and 19 males (43.2%), mean age of 7.93 ± 4.74 months. The healthy controls included 13 females (54%) and 11 males (46%), mean age of 24.6 ± 20.49 months. See Table 1.

Skin prick test

Skin prick tests were performed on the volar aspect of the forearm with commercial extract of the suspected food from ALK Abello™ (Port Washington, NY, USA). All tests

Table 1 Study population

Group	Positive CMPU	Negative CMPU
A IgE CMA, non-AD patients (n = 68)	37% (25/68)	63% (43/68)
B IgE CMA, AD patients (n = 21)	71% (15/21)	29% (6/21)
C Non-IgE CMA, non-AD patients (n = 41)	0% (0/41)	100% (41/41)
D Non-IgE CMA, AD patients (n = 3)	0% (0/3)	100% (3/3)
E Healthy controls (n = 24)	0% (0/24)	100% (24/24)

CMA, cow's milk allergy; AD, atopic dermatitis; CMPU, contact milk protein urticaria.

included a positive control with histamine (1 mg/ml) and a negative control with saline (ALK Abello). Wheals with a mean diameter ≥ 3 mm than those of the negative control were considered positive reactions (8).

CMP challenge

Challenge to CMP was performed using infant formula (Materna; Maabarot Products Ltd, Maabarot, Israel) or cow's milk by introducing increasing doses from 1.0 ml to 2.5 ml, 5 ml, 10 ml, 20 ml, 40 ml, and 80 ml every 20–30 min. The challenge was ended if a cutaneous, respiratory, gastrointestinal, or systemic response was observed. Patients were considered tolerant if no allergic symptoms appeared after a week of ingesting cow's milk products.

CMA contact test ('finger test')

All patients with a history of either IgE or non-IgE CMA were exposed to pure cow's milk (Tnuva, Israel; fat content 3%, protein content 3.3%) in its ordinarily consumed state on one cheek in an area where the skin was intact and non-injured.

Specifically, the physician placed his/her finger in the milk and then applied a drop on the subject's cheek, hence the name 'finger test'. Accordingly, this testing may be regarded as a slight modification of the initial step described by Krogh and Maibach for the evaluation of allergic contact urticaria (9). It was interpreted as positive if a flare and wheal reaction developed within 20 min at the spot where the milk was applied (see Fig. 1).

Data collection

The study was based solely on observational data gathered in the course of patient care and was approved by the Helsinki Review Board of Bnai Zion Medical Center. Informed consent was obtained from all patients and controls.

Statistical analysis

Data for continuous variables with normal distribution were expressed as mean $\pm$ s.d. and analyzed using the Student's *t*

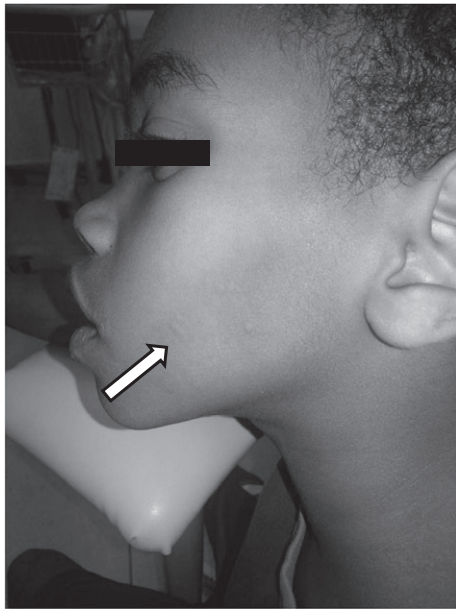


Figure 1 Cow's milk contact urticaria (positive finger test). Application of cow milk protein on the cheek of a child by physician's finger, lead to the appearance of flare and wheal reaction (white arrow) developed within 20 min at the spot where the milk was applied.

test. For pairwise comparisons of categorical data between groups, we used Fisher's exact test (two-tailed). All *p*-values <0.05 were considered significant.

Results

Of the 89 patients with IgE-mediated CMA, 40 (44.9%) had a positive reaction to the finger test – namely, appearance of contact urticaria at the area of milk application – while 49 had a negative reaction. The difference in mean age between the children with a positive contact reaction (31.9 ± 40.1 months) and those with a negative reaction (28.4 ± 44.9 months) was not statically significant (*p* = n.s).

The IgE-mediated group was further divided into two subgroups according to the presence of AD (Table 1, groups A + B). Twenty-one of the 89 patients (23.6%) had IgE-mediated CMA with AD. Of these, 15 tested positive for contact urticaria to cow's milk (71%) and six tested negative (29%). The second subgroup, the IgE-mediated CMA non-AD patients, comprised 68 patients (76.4%), of whom 25 tested positive (37%) and 43 tested negative (63%). Urticaria was the main presenting symptom of IgE-mediated CMA allergy in groups A + B (Table 2).

Thirty-five of the 89 patients (39.3%) with IgE-mediated CMA (groups A + B) had a history of family atopy (asthma, allergic rhinitis or food allergy in a first-degree relative), with a higher percentage in those with positive contact urticaria to cow's milk: 21 of 40, or 52.5% of those with a positive finger

test, vs. 14 of 49, or 28.5% of those with a negative finger test; *p* = 0.029 (Table 2).

Twenty-seven of the 89 children with IgE-mediated CM allergy had multiple food allergies, as indicated by positive SPTs with compatible clinical history for other foods, especially sesame seeds, eggs, and tree nuts. With regard to the relationship between a positive contact reaction to milk protein and multiple food allergies in IgE-mediated CMA patients (groups A + B), we found that 20 of the 40 patients with a positive reaction (50%) had multiple food allergies compared to only seven patients of the 49 (14.3%) with a negative reaction, *p* = 0.004.

In the group of patients with IgE-mediated milk allergy with positive contact reactions to cow's milk and multiple food allergies (20 patients), almost half had AD. However, in the AD group (21 patients), the incidence of patients with positive contact reactions to milk and multiple food allergies was significantly higher than among those patients without AD: 9 of 21 (42.8%) vs. 11 of 68 (16.1%), *p* = 0.0165; Table 2.

Twenty-seven of the 89 patients with IgE-mediated milk allergy had multiple food allergy (30.3%). Of them, 70.37% (19/27) had allergy to two foods, 25.93% (7/27) had allergy to three foods, and 3.7% (1/27) had allergy to four foods (see Table 3).

Looking into the additional types of food allergies, we found that 13 patients were allergic to egg (48.1%), 13 (48.1%) were allergic to sesame seeds, and four had allergy to peanut (14.8%). Twelve of 13 patients with sesame allergy (92.3%) had positive contact reactions to milk in comparison with patients with egg allergy, which only 7 of 13 (53.8%) had positive contact reaction with CMP (*p* = 0.07). Other food allergies that were found are detailed in Table 3.

None of the subjects with non-IgE-mediated CMA had positive contact reactions to cow's milk, including the three patients with AD (Table 1, groups C + D).

Similarly, none of the 24 healthy individuals tested positive in the finger test (Table 1, group E). We found no correlation between the SPT diameter size and a positive finger test.

Discussion

The reaction of wheal and flare from direct contact with a chemical or protein agent is known as contact urticaria. Back in 1981 Geo Von Krogh described that food allergens may penetrate into intact skin, triggering immunologic contact urticaria (9). Almost any food is capable of eliciting an immunologic contact urticaria. The main aim of this study was to assess the significance of cow's milk contact urticaria in a large group of patients with CMA.

Contact urticaria to food, and cow's milk specifically, was reported and studied previously mainly in patients with AD (6, 7). Our first observation confirmed that contact urticaria to CMP exists only in patients with IgE-mediated CMA, regardless of the presence of AD. Of 89 IgE-mediated CMA patients, 40 (44.9%) developed positive contact urticaria. We found that

Table 2 Patients' characteristic

Characteristics	IgE CMA, non-AD patients (n = 68)		IgE CMA, AD patients (n = 21)	
	Positive CMPU (n = 25)	Negative CMPU (n = 43)	Positive CMPU (n = 15)	Negative CMPU (n = 6)
Age average (months)	38.3	29.8	32.3	56.3
Sex (male:female)	13:12	21:22	8:7	4:2
CMA symptoms				
Urticaria	92% (23/25)	86% (37/43)	87% (13/15)	67% (4/6)
Angioedema	8% (2/25)	7% (3/43)	20% (3/15)	0% (0/6)
Hoarseness	0% (0/25)	2.3% (1/43)	0% (0/15)	0% (0/6)
Dyspnea	4% (1/25)	0% (0/43)	6% (1/15)	33% (2/6)
Anaphylaxis	8% (2/25)	0% (0/43)	0% (0/15)	17% (1/6)
Family atopy	40% (10/25)	28% (12/43)	73% (11/15)	33% (2/6)
Other food IgE-mediated allergies	44% (11/25)	12% (5/43)	60% (9/15)	33% (2/6)

CMA, cow's milk allergy; AD, atopic dermatitis; CMPU, contact milk protein urticaria.

Table 3 Frequency of allergies to specific foods in the study population

Food	Patients without AD		Patients with AD	
	Positive CMPU	Negative CMPU	Positive CMPU	Negative CMPU
Milk	14	38	6	4
Milk, sesame	5	1	3	
Milk, egg	1	2	1	1
Milk, peanut			2	
Milk, nut		1	1	
Milk, fish			1	
Milk, sesame, egg	3		1	
Milk, egg, nut	1			
Milk, egg, fish	1			
Milk, egg, peanut				1
Milk, egg, nut, peanut		1		
Total number	25	43	15	6

AD, atopic dermatitis; CMPU, contact milk protein urticaria.

children with IgE-mediated CMA with AD had statistically higher allergic contact urticaria to CMP compared to children without AD [71.4% (15/21) vs. 36.7% (25/68), $p = 0.0064$]. This may be explained by the nature of the inflamed skin in AD, which allows better penetration of the CMP and intense reaction due to a complex interaction between various susceptibility genes, defects in skin barrier function, and immunologic responses (10). Specifically, in patients with AD, skin barrier impairment may facilitate the epicutaneous penetration of molecules of food and environmental allergens. This physiologic impairment results from reduced levels of stratum corneum lipids; defects in proteases, antiproteases, or both and acquired or genetic defects in structural proteins, such as filaggrin and loricrin (11). It was also shown that in AD, direct contact of food allergens with the skin might be an important factor for the aggravation of eczema (12). Contact urticarial lesions can also be provoked in normal skin (non-eczematous) by lipophilic allergens that may penetrate the skin via the hair follicles (13). Contact with food protein without ingestion can

also cause severe systemic allergic reactions (5, 14). Tan et al. described five cases of children who experienced severe food allergic reactions by trivial skin contact to milk and peanuts. They were characterized by strong family history of allergy, early age of onset, and a strong positive reactivity to foods by SPT. Interestingly, all of them suffered from multiple food allergies (5).

The prevalence of atopic diseases is high among parents of allergic individuals, especially those with food allergies, compared to healthy individuals (1). In our study, we found a higher rate of atopic disease in first-degree family members among children with positive contact urticaria to CMP compared to children with a negative finger test (groups A + B). We did not find these differences when we assessed each group separately (with and without AD), probably due to the small number of patients. Food allergy seldom occurs to just one food. A progression from milk and/or egg allergy in early infancy to additional food allergies, for example peanut, is common (15). In a randomized, cross-sectional survey that was administered electronically to a representative sample of US households with children. Food allergy prevalence was 8.0%; among them, 30.4% had multiple food allergies (16).

In a cross-sectional study from Israel among infants and young children under the age of 2 yr, 61.5% were allergic to one food, 27% to two foods, and 11.5% to three or more foods (17).

Similarly, we found that 27 patients of our patients with IgE-mediated CMA (27/89, 30.3%) had multiple food allergies. We observed that multiple food allergies were more prevalent with positive CMP contact urticaria. Twenty of these patients (20/27, 74%) had positive contact urticaria to CMP.

According to our findings, patients with a positive finger test to CMP who had IgE-mediated CMA had significantly more additional food allergies compared to children with a negative finger test (50%, or 20/40, vs. 14.2%, or 7/49; $p = 0.0004$) (Table 2). This finding was also statistically significant in group A, which consisted of children with IgE-mediated CMA without AD (44%, or 11/25, vs. 12%, or 5/43, $p = 0.006$). In group B, we did not find this difference, most likely due to the

small number of patients. Interestingly, the most common food allergy in patients with positive contact urticaria to CMP was sesame seeds (Table 3), and not egg or tree nuts as commonly reported (1).

Geographical differences in the rates and specific types of food allergies have been observed. Specifically in Israel, sesame is a major cause of IgE-mediated food allergic reactions. It was reported to be second only to cow's milk as a cause of anaphylaxis and third as an overall cause of IgE-mediated food allergy (17). Like CMA, sesame allergy is displayed early in life and can cause severe allergic reactions, and tolerance develops in only 20% of affected individuals (18, 19). Although it is known that sesame seeds are commonplace in Israel, this study marks the first association of sesame with milk protein allergy and contact urticaria. The source for this association may lie in

some combination of genetics, ethnicity, and the food consumption culture prevalent in the sample studied.

Our study had a number of limitations. Some of our subgroups were small, and for ethical reason, we did not perform an oral food challenge in all cases. Our patients had strongly positive skin test reaction to a cow milk extract and specifically children under the age of 2 yr had a recent documented clinical which cause us to defer oral food challenge (20).

In conclusion, we found contact urticaria to CMP to be common even in children without AD, with a strong association between contact urticaria and multiple food allergies. A positive finger test to CMP as part of the evaluation of CMA patients suggests the potential for multiple food allergies, especially to sesame and egg.

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