

Lessons from the clinical course of IgE-mediated cow milk allergy in Israel

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Cow milk and milk products are the most common food products consumed in Israel; rates of allergy to cow milk exceed those of peanuts in infants and children. The aim of the present study was to evaluate retrospectively the clinical features and natural course of immunoglobulin (Ig) E-mediated cow milk allergy (CMA) in Israel. Data of children diagnosed with CMA from 1995 to 2003, were collected regarding age at first and most recent reactions, symptoms and signs, family history of atopy, other allergic diseases, emergency department visits, hospitalizations, and treatment. Patients with transient CMA were compared to those with persistent CMA (≥ 3 yr old). The study group consisted of 105 patients, 43 with transient CMA (age range: 0.48–11 yr). The remaining 62 patients (age range: 3–16.5 yr) did not achieve tolerance to cow milk during the follow-up period. No differences were found between the groups in mean age and symptoms and signs at the first allergic reaction and family history of atopy. Patients with persistent CMA had a higher rate of asthma than patients with transient CMA (61.2% vs. 18.6%, $p < 0.001$). Fifty patients with persistent CMA had 137 subsequent allergic reactions after diagnosis, 25% of the reactions were due to oral milk challenge at the clinic and 75% due to accidental exposure, of which 13% required an emergency department visit and 8%, hospitalization. Only 19% of the reactions were treated with epinephrine injection. In conclusion, in our experience, less than half of the children diagnosed with IgE-mediated CMA during 9 yr, outgrew it. The patients with persistent CMA have a higher prevalence of asthma compared with the general population or to children with transient CMA. The high number of recurrent allergic reactions due to accidental exposure and the low rate of epinephrine usage in these patients point to a need for better education of patients and their families.

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In Israel, the biblical 'land of milk and honey' the most frequent food consumed by the population is cow milk. During 2005, the average consumption per month of cow milk drinks and products in Israel was 55,000,000 l (<http://www.milk.org.il>), giving an annual consumption of 110 l per person. Accordingly, milk-induced allergic reactions exceed peanut-induced allergic reactions; in the 0- to 2-yr age group, Dalal et al.

found the rate of allergy to cow milk to be 0.3% as opposed to 0.04% for peanuts (1).

The aim of the present study was to define the clinical characteristics of immunoglobulin (Ig) E-mediated cow milk allergy (CMA) in children in Israel and to assess its natural course. The medical literature was reviewed and our findings were compared with the reports from other countries.

Patients and methods

The study group consisted of children and adolescents treated at our allergy clinic for IgE-mediated CMA from January 1995 to December 2003. The diagnosis of CMA was made on the basis of an unequivocal immediate allergic reaction to cow milk and evidence of specific IgE antibodies to cow milk by skin prick test and/or blood tests. Skin prick tests were performed with saline as the negative control and histamine (1 mg/1 cm³) as the positive control (ALK Ab  llo, Port Washington, NY, USA). Mean wheal diameter of 3 mm greater than the negative control was considered positive. Serum cow milk-specific IgE antibodies were detected by the AlaSTAT (up to year 2002) and Immulite methods (DPC, Los Angeles, CA, USA).

The patients were followed once yearly with open-oral milk challenge as previously described (2), except in cases of an immediate allergic reaction to cow milk because of accidental exposure shortly before the scheduled visit. The study group was divided into transient and persistent CMA groups; persistent CMA was defined as an immediate allergic reaction to open-oral challenge or due to accidental exposure at the age of 3 yr or older. Children who were documented to consume milk safely were included in the transient CMA group. The patient files were reviewed for age at the first and the most recent allergic reactions, symptoms and signs of the allergic reaction, additional allergic diseases (allergic rhinitis, bronchial asthma, atopic dermatitis, other food allergies), family history of atopy, emergency department visits and hospitalizations, and treatment.

Findings were compared between the two subgroups using analysis of variance, Pearson chi-squared test and Fisher's exact test, as appropriate. A p-value of <0.05 was considered significant. All statistical analyses were performed with BMDP statistical software.

Results

The study population included 105 patients; 43 with transient CMA (age range: 0.48–11 yr, mean duration of follow-up: 2.71 ± 2.24 yr), and 62 patients with persistent CMA (age range: 3–16.5 yr, mean duration of follow-up: 5.13 ± 3.88 yr). Of the 43 patients with transient CMA, 20 children achieved tolerance to milk up to age 3 yr, 13 up to the age of 5 yr, seven up to the age of 9 yr, and three up to the age of 11 yr. None of the patients in the persistent CMA

Table 1. Clinical data of children with persistent and transient CMA

	Persistent CMA (n = 62)	Transient CMA (n = 43)	p-Value
Male/female	41/21	23/20	NS
Age at first allergic reaction (months)			
Range	0.25–12	0.1–15	NS
Mean	4.9 ± 2.69	4.03 ± 2.99	
Atopic family history, n (%)			
Bronchial asthma	17 (27.4)	7 (16.2)	NS
Atopic dermatitis	3 (4.8)	1 (2.3)	NS
Allergic rhinitis	7 (11.2)	7 (16.2)	NS
Food allergies	6 (9.6)	1 (2.3)	NS
Additional allergic diseases, n (%)			
Bronchial asthma	38 (61.2)	8 (18.6)	<0.001
Atopic dermatitis	15 (24.1)	4 (9.3)	NS
Allergic rhinitis	2 (3.2)	1 (2.3)	NS
Other food allergies*	10 (16.1)	4 (9.3)	NS

NS, not significant; CMA, cow milk allergy.

*Other food allergies: eggs – 2 patients; peanuts – 4; sesame – 3; nuts – 1; fish – 1; corn – 1; peach – 1.

group achieved tolerance at the time of the data collection.

The persistent group had a higher male/female ratio (2:1), but the difference did not reach statistical significance (Table 1). No between-group differences were found in mean age at first allergic reaction or family history of atopy (Table 1). Comparison of other allergic diseases revealed a significantly higher prevalence of asthma in the patients with persistent CMA (61.2%) than in those with transient CMA (18.6%, $p < 0.001$; Table 1).

Most of the patients with persistent CMA in this study (80.5%) were aged 3–9 yr at the most recent allergic reaction (Table 2). Although there were no differences in the clinical presentation at the first allergic reaction between the patients with transient and persistent CMA (Table 3), the patients with persistent CMA presented with a different clinical picture at their first allergic reaction and at their most recent one. Nine patients (14.5%) had a change of consciousness

Table 2. Age distribution of children with persistent cow milk allergy at the most recent allergic reactions*

Age group (yr)	N (%)
3–5	29 (46.7)
5–7	8 (12.9)
7–9	13 (20.9)
9–11	5 (8)
11–13	1 (1.6)
13–15	3 (4.8)
15–17	3 (4.8)
Total	62 (100)

*Due to accidental exposure or on oral challenge at the clinic.

Table 3. Clinical presentation of the allergic reactions in children with persistent or transient cow milk allergy (CMA)

Clinical presentation	Transient CMA at first reaction, n (%)	Persistent CMA	
		At first reaction, n (%)	At most recent reaction, n (%)
Vomiting	19 (44.1)	26 (41.9)	13 (20.9)
Urticaria/rash	32 (74.4)	51 (82.2)	31 (50.0)
Angioedema	9 (20.9)	19 (30.6)	17 (27.4)
Shortness of breath/wheezing	4 (9.3)	14 (22.5)	22 (35.4)
Apathy/hypotension	—	—	9 (14.5)

p-Value – not significant for all parameters.

and/or documented hypotension at their last reactions, whereas none do so at the first (Table 3). The prevalence of respiratory tract involvement also increased from 22.5% to 35.4%, whereas the rate of urticaria and rash decreased from 82.5% to 50%, although these differences did not reach statistical significance (Table 3).

Table 4 shows that the 50 patients with persistent CMA had a total of 137 subsequent allergic reactions. Twenty-five percentage of the reactions occurred during oral challenge at the clinic, and 75% on accidental exposure, leading to emergency department visits in 13% of the reactions and admission to hospital in 8%.

Only 19% of the reactions were treated with epinephrine injections (Table 5); almost all the injections were given by medical staff, and not by the patients/parents (data not shown). There were no fatalities.

Table 4. Subsequent allergic reactions to cow milk in 50 children with persistent cow milk allergy during 1995–2003

Type of reaction	Reactions, n (%)	Patients (n)
Positive oral challenge at the clinic	34 (25)	20
Accidental exposure		
Resolved at home	74 (54)	39
Emergency department visit	18 (13)	12
Hospitalization	11 (8)	7
Total	137 (100)	

Table 5. Treatment of 137 subsequent allergic reactions in children with persistent cow milk allergy (CMA)

Treatment	Persistent CMA, n (%)
Antihistamines	86 (62.7)
Systemic corticosteroids	42 (30.6)
Bronchodilators	49 (35.7)
Epinephrine injection	26 (18.9)
No treatment	4 (2.9)

Discussion

The present study showed that of 105 children with IgE-mediated CMA followed at our clinic during 1995–2003, only 43 (41%) achieved clinical tolerance to milk during the follow-up period of 9 yr. Previous studies from Australia and Denmark demonstrated tolerance to cow milk in 28–77% of patients with CMA by 2 yr of age, 56% by 4 yr, 78–92% by 6 yr, and 97% by 15 yr (3, 4). Another study of 115 children in Italy found the median age for tolerance to cow milk to be 7 yr and 11 months (5). These differences may be explained by our inclusion of a selected population with CMA referred to a tertiary medical center. In addition, one of the previous studies did not differentiate between IgE and non-IgE-mediated CMA, the latter typically resolves during the first two years of life (4). It is also possible that ethnic and genetic variations play a role in the development of oral tolerance to cow milk (6).

The patients in the present study with transient or persistent CMA were of similar age at the first allergic reaction and had a similar family history of atopy (Table 1); there was a greater, but statistically non-significant male predominance in the group with persistent CMA (Table 1). This finding is consistent with the previous reports of a higher prevalence of atopic diseases and asthma in males up to adolescence (7–9). Male gender has not been studied as a risk factor for persistence of CMA, but a telephonic survey in the United States indicated a male predominance for peanut/tree nut allergy in children younger than 18 yr (10).

The children with persistent CMA had a higher prevalence of asthma (61.2%) than those with transient CMA (18.6%), and both groups had a higher prevalence of asthma than the general Jewish population in Israel (7.8% in 7436, 13–14 yr olds; 11). Accordingly, a study from Portugal reported that children with CMA, regardless of its duration, had a higher risk of developing asthma and rhinitis than the general pediatric population of the country, and the children with persistent CMA had a higher prevalence of asthma than the children with transient CMA (12). Other groups noted a higher prevalence of asthma in Italian children with persistent CMA compared with controls (13), and a 41% prevalence of asthma in children with CMA younger than 10 yr in Denmark (4).

The association between these disorders is supported by recent studies showing that food allergy is a significant risk factor for life-threatening asthma (14) and that patients with

near-fatal asthma report more food allergies, with onset of asthma episodes following a visit to a bar, party, or restaurant (15).

There were no significant differences in the clinical presentation at the first allergic reactions between the two groups, or even between the first and most recent allergic reaction in the patients with persistent CMA (Table 3). Nine patients (14.5%) with persistent CMA had a change of consciousness and/or documented hypotension at their last reaction, compared with none at the first reaction, but this may be related to the different ages of the patients at the time of the reaction and observer bias.

Of the 137 subsequent allergic reactions in 50 patients with persistent CMA, 75% were due to accidental exposure and 8% warranted hospital admission (Table 4). A study from the United States also found that children with severe IgE-mediated CMA in infancy had more episodes of sudden severe anaphylaxis and hospitalizations compared to a group of atopic children without CMA (16).

No fatal milk-induced allergic reactions occurred. This is in contrast to data from the United States, where one of 32 food-induced fatal anaphylactic reactions was due to milk (17), and data from the UK, where four of eight fatal food-induced anaphylactic reactions during 10 yr were due to milk (18).

The absence of fatal milk induce allergic reactions in our series is encouraging. The routine management of the patients include their education to read food labels and to inject EpiPen if needed. It is known that fatal food induced anaphylactic reactions usually occur outside medical facilities (17, 18). Most of the reactions due to accidental exposure to milk in our patients resolved at home and only 21% reached hospitals. We assume therefore that fortunately most reactions were mild, a fact which together with the easy and quick access to emergency medical services in Israel in case of more severe reactions, may explain the absence of fatalities in our series. However, the high number of allergic reactions due to accidental exposure, combined with the low rate of EpiPen use by the patients and families, indicate a low awareness of the severity and potential fatal outcome of food allergy in Israel. Thus, given our finding that more than half of all affected children may still have CMA by school age, we recommend that special precautions be taken by the school staff in Israel, along with guidelines for the management of life-threatening food allergies developed in some states in the United States (19). These guidelines have recently been

published by the Israel Ministry of Education (<http://www.education.gov.il/mankal>, accessed on September 2004). In addition, educational programs for patients and parents should be implemented by the pediatric allergists together with training of the use of the EpiPen in order to ensure the proper emergency management of children with persistent CMA in case of accidental exposure. A recent study has shown that the empowerment of the parents directly correlated with their increased comfort with EpiPen use (20).

In conclusion, in our experience, more than half of the children with IgE-mediated CMA will not outgrow it by 3 yr of age, and these patients have a high prevalence of asthma compared with the general population and also to children with transient CMA. Given the fact that cow milk drinks and other products are very popular in Israel, special precautions and guidelines must be implemented by the authorities, professionals and the families, for the prevention and management of life-threatening exposure.

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