



# IgE-Mediated Cow's Milk Allergy in Iranian Infants and Children: Predictive Factors of Early Tolerance

Mohammad Hossein Eslamian,<sup>1,2</sup> Mozhgan Moghtaderi,<sup>3</sup> and Mohammad Gharagozlou<sup>1,4,\*</sup>

<sup>1</sup>Allergy and Clinical Immunology Division, Children's Medical Center, Pediatrics Center of Excellence, Tehran, Iran

<sup>2</sup>Department of Pediatrics, Allergy and Clinical Immunology Division, Hamadan University of Medical Sciences, Hamadan, Iran

<sup>3</sup>Allergy Clinic of Aliasghar Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>4</sup>Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran

\*Corresponding author: Mohammad Gharagozlou, Allergy and Clinical Immunology Division, Children's Medical Center, Pediatrics Center of Excellence, No 62, Dr Gharib St., Tehran, Iran. E-mail: gharagoz@tums.ac.ir

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## Abstract

**Background:** The majority of infants and children with cow's milk allergy will grow out of their allergy after a few years. The aim of this study was to identify the natural course of cow's milk allergy in infants and children during a follow-up of 18 months and also the predictive factors for its outgrowing.

**Methods:** This prospective cross-sectional study included infants and children with IgE-mediated cow's milk allergy. Demographic data, clinical manifestations and probable predictive factors were recorded. Skin prick tests were done with commercial extracts of cow's milk, egg, fish, nuts and wheat on arrival. These infants and children were followed for 18 months and resolution was established by successful ingestion of cow's milk. The collected data were analyzed using SPSS version 22.0. Descriptive statistics, student's t-test or Mann-Whitney U-test and Chi-square test were used; a  $P < 0.05$  was considered statistically significant.

**Results:** Forty-nine infants and children (33 boys and 16 girls) with IgE-mediated cow's milk allergy presentation ranged in age from 3.5 to 48 months with a mean of  $17.5 \pm 11.7$  months enrolled in this study. Skin was the most common site of involvement, followed by gastrointestinal system and respiratory tract. Twenty-three (46%) infants and children developed tolerance to cow's milk during a follow-up of 18 months. There was a significant relationship between parental allergy and atopic dermatitis with the chance of tolerance of cow's milk.

**Conclusions:** Our findings showed that about one half of the infants and children with IgE-mediated cow's milk allergy grew out of it over 18 months of follow-up (mean age 2 years). The follow-up of patients with cow's milk allergy is important in appropriate timing of re-introduction of cow's milk to the diet; atopic dermatitis and parental allergy can predict this outcome.

**Keywords:** Milk, Food Allergy, Immunoglobulin E, Prognosis, Tolerance, Iran

## 1. Background

Cow's milk is one of the most common food allergens, and nearly all infants and children with IgE-mediated cow's milk allergy (CMA) show their symptoms within a few minutes to weeks after they are first given cow's milk (1, 2). The clinical symptoms of CMA often are related to skin, gastrointestinal tract and rarely respiratory system; however, the severity of symptoms varies from mild involvement in an organ to serious life-threatening reaction and anaphylaxis (3, 4). Most children with CMA outgrow their milk hypersensitivity within a few years; 56% by age 1 year, 77% by age 2 years, 87% by age 3 years and 92% at 5 years (5). Although most children with CMA will tolerate their allergy, the precise time of resolution varies among countries (2, 6).

Many studies have shown that the rate of CMA resolu-

tion is widely different in various populations (7, 8); however, determining natural history of CMA is highly related to the immunological and clinical phenotypes (9). Children with IgE-mediated (immediate reaction) CMA tend to outgrow at a later age and at fewer numbers compared to those with non IgE-mediated (delayed) reaction. Tolerance to cow's milk (CM) will occur later among children who initially showed severe clinical reactions such as asthma (6, 10). Predictive factors are different between studies; no single marker has been consistently found to be predictive of tolerance to CM yet.

The best method for confirming or excluding CMA is the oral challenge test which is rarely suggested in the neonatal period because of probable complications (11). Therefore, the diagnosis of CMA is usually based on the skin prick test (SPT) with standard commercial extracts or with

fresh milk as prick to prick or measurement of milk serum specific IgE level (e.g. Radioallergosorbent test: RAST). SPT is a simple, safe, inexpensive and less time-consuming tool used for the evaluation of patients with CMA. Meanwhile, it is reported that reduction in SPT size in the periodic re-evaluation of a patient with CMA may be a factor in predicting of tolerance to milk. Measuring milk serum IgE has become popular in recent years, but the production of all immunoglobulin classes and especially IgE is reduced in the neonatal period (11, 12).

Few studies on the prevalence of CMA and natural history of IgE-mediated CMA have been undertaken in Iran. This study was designed to determine the time of growing out of it during a follow-up of 18 months and to identify the related predicting factors in Iranian infants and children with IgE-mediated CMA.

## 2. Methods

This prospective cross-sectional study was performed on infants and children with IgE-mediated CMA who were referred to allergy clinic at children's medical center of Tehran during the years 2013 - 2014. Enrollment required the parents' description of the immediate allergic symptoms after giving CM to their infants and children at the time of study accompanying with positive SPT result to CM. Informed consent was obtained from their parents and the study protocol was approved by Tehran University's ethics committee. Infants and children with non IgE-mediated CMA based on negative SPT to cow's milk were excluded in this study.

A questionnaire was developed containing information on age, sex, birth date, mode of delivery, age of mother during pregnancy, birth weight, age at onset of allergy symptoms to milk, parental education, parental allergy, parental consanguinity, duration of breast feeding, age at the introduction of solid food, and having atopic dermatitis. Self-reported parental allergy was defined if at least one parent suffered from allergy. Itchy skin rash and urticaria were considered as the cutaneous symptom; wheezing and breathing difficulty and rhinorrhea as pulmonary symptoms; and diarrhea and vomiting as gastrointestinal manifestations. Symptoms were considered CMA-related if they started after the ingestion of milk. Ingestion of CM was firmly restricted in the studied infants and children and they received hydrolyzed formula. Mothers of breastfed infants and children avoided using CM and its products.

Commercial cow's milk, egg, fish, nut and wheat extract (Greer, Lenoir, NC, USA) were administered on the forearm of the infants and children for SPT. Normal saline and histamine (10 mg/mL) was used as negative and positive controls, respectively. The results of the skin tests were

examined after 15 minutes and considered positive when the wheal diameter was  $\geq 3$  mm larger than the negative control, respectively. SPT was done at the baseline for these five allergens. We asked the parents not to take antihistamine medication to their infants and children for 5 days and topical corticosteroids for one day before the procedure.

The parents were asked to refer to outpatient clinic every 3 months for recording the subjects situation and doing SPT to CM in their infants and children when necessary. Patients, mostly after the age of 12 months, who had a negative SPT to cow's milk, were challenged with uncooked cow's milk under supervision of a physician in the hospital.

### 2.1. Statistical Analysis

All data were analyzed using SPSS version 22 (SPSS Inc.; Chicago, IL, USA). Data were mentioned as mean  $\pm$  standard deviation (SD). The relationship between independent and dependent variables was compared using the student's t-test or Mann-Whitney U-test and the prevalence of variables by Chi-square test. A P value of  $\leq 0.05$  was considered significant.

## 3. Results

Of the sixty signed up infants and children with the diagnosis of CMA at baseline, forty-nine infants and children (3.5 - 48 months, mean age  $17.5 \pm 11.7$  months) with IgE-mediated CMA were enrolled in the study for 18 months. Male to female ratio was 33 to 16. Mean birth weight of these infants and children was  $3.2 \pm 0.5$  Kg. The age of onset of allergy symptom to cow's milk was from the first day after birth to 7 months of age (mean age  $2.9 \pm 2.4$  months).

At a follow-up of 18 months, the result of SPTs to cow's milk was negative in 23 (46%) infants and children. Tolerance to CM was confirmed in these patients via an open challenge test with uncooked CM in the hospital. Mean age of the infants and children who developed resolution was  $22.08 \pm 10.33$  months at the time of resolution.

Characteristic data on infants and children with IgE-mediated CMA, comparing those with and without milk allergy resolution, are shown in Table 1. There was a significant relationship between parental allergy and existence of atopic dermatitis with the chance of non-tolerance to CM.

There was a history of allergic disease in 10 mothers; allergic rhinitis in 6, atopic dermatitis in 2, and asthma and food allergy each in one mother. Allergy was found in 8 fathers; 7 allergic rhinitis and 1 atopic dermatitis. None of the mothers had a history of smoking.

**Table 1.** Comparison of the Baseline Characteristic Data on Infants and Children with IgE-Mediated Cow's Milk Allergy with Resolution and Without Resolution

Parameters	Children with Cow's Milk Allergy		P Value
	With Resolution, n = 23	No Resolution, n = 26	
<b>Gender</b>			0.3
Male	14	19	
Female	9	7	
<b>Age (month)</b>			0.1
< 18	15	12	
≥ 18	8	14	
<b>Birth weight (Kg)</b>			0.2
< 3.5	18	16	
≥ 3.5	5	10	
<b>Months of birth</b>			0.7
Oct - Mar	10	10	
Apr - Sep	13	16	
<b>Onset of allergy symptom (months)</b>			0.2
< 1	10	7	
≥ 1	13	19	
<b>Parental allergy</b>			0.01
Yes	12	5	
No	11	21	
<b>Advance educated parents</b>			0.1
Yes	14	10	
No	9	16	
<b>Type of delivery</b>			0.9
Cesarean section	17	15	
Vaginal delivery	6	11	
<b>Exclusive breast fed</b>			0.7
Yes	22	25	
No	1	1	
<b>Skin symptoms at onset</b>			0.06
Yes	14	22	
No	9	4	
<b>Consanguinity between parents</b>			0.9
Yes	5	6	
No	18	20	
<b>Father smoker</b>			0.6
Yes	1	2	
No	22	24	
<b>Size of prick test to cow's milk (mm)</b>			0.3
3 - 10	16	21	
> 10	7	6	
<b>Positive prick test to egg</b>			0.5
Yes	9	8	
No	14	18	
<b>Introduction of solid food &lt; 6 months</b>			0.1
Yes	1	5	
No	18	18	
<b>Atopic dermatitis</b>			0.05
Yes	8	3	
No	15	23	
<b>Age of first reaction to milk (month)</b>			0.1
≤ 1	11	7	
> 1	12	19	

Among 49 infants and children with IgE-mediated CMA, clinical symptoms of allergy were cutaneous manifestations in 36 infants and children (19 cases of eczema, 14 urticaria and 3 presenting eczema and urticaria) and these were followed by gastrointestinal symptoms in 10 infants and children (6 cases of repeated vomiting, 2 cases

of chronic diarrhea) and respiratory symptoms in 5 infants and children (wheeze and breathing difficulty). Two patients had combinations of skin and gastrointestinal symptoms.

In a decreasing order of frequency, positive SPT was seen to egg in 17 (34.6%), nuts and wheat in 3 (6% each), and

fish in 2 (4%) cases.

All children with negative SPT ingested fresh uncooked CM without any reaction at 18 months of the follow up.

#### 4. Discussion

The natural history of CMA is favorable and determining the individual timing of tolerance acquisition is critical for clinicians and anxious parents. This study found that about one half of infants and children with immediate type of CMA grew out of their allergy over 18 months of follow up. A wide range of CMA resolution rates has been reported from studies examining the natural history of CMA in different countries (6, 9, 13). In 9 European countries, 69% of children with CMA tolerated cow's milk one year after diagnosis, and all children with non IgE-mediated CMA and 57% of those with IgE-mediated CMA did so (14). A large cohort of 512 infants and children with CMA ranging from 3 to 15 months of age at 5 areas of the USA demonstrated a resolution rate of about 50% by age 5 (15). A natural course of CMA in 115 Korean children < 24 months of age with atopic dermatitis showed 50% tolerance at 67 months of age (16). It is, therefore, nearly similar with other studies although the study design, age of infants and children, unselected group of children with immediate type CMA, and the time of follow up were different.

Variables such as sex, age, birth weight and birth month were not predictors of developing tolerance to cow's milk in the present study.

Age of first reaction to CM in our children was not related to the course of CMA. In contrast to our finding, Elizur et al showed that 54 infants and children with CMA who developed their first reaction to milk in the first month of life were at highly increased risk for persistence of allergy (17).

Goldberg et al revealed no relationship between atopic status of parents in infants and children with IgE-mediated CMA and the control group (18). Parental allergy remained a strong predictor of developing tolerance in our patients. It is noticeable that self-reporting of atopy by parents may be biased.

Similar to our result, several studies found a relationship between atopic dermatitis and intolerance to cow's milk in CMA infants and children; however, moderate to severe type of atopic dermatitis was associated with a lower likelihood of developing tolerance (15, 16). History of sensitization to certain foods such as egg has been reported with a worse prognosis in early life, but no significant association with intolerance to cow's milk was observed in this study (9).

Children with IgE-mediated CMA have a greater risk for other atopic diseases than those with non IgE-mediated

CMA (5). In this study, 73.4% of the children suffered from eczema, while 50% had at least 1 other food sensitization, 20.4% had gastrointestinal manifestations, and 10.2% respiratory symptoms, although these rates of gastrointestinal manifestations and respiratory symptoms are lower than those reported in previous studies (6, 9).

The baseline SPT wheal size to milk was not effective in prediction of resolution to milk in the present study (P value = 0.3); this is different from the study by Wood et al who found SPT wheal size to milk as the most important factor in predicting resolution of milk allergy (15).

A Greek study reported that the negative result of pre-challenge SPT to milk could properly predict a negative challenge outcome in agreement with our study (19).

Liao et al. compared exclusive breastfeeding in infants and children < 4 months with those  $\geq$  4 months and showed a decreased risk of sensitization toward CMA up to the age of 2 years in long time breast feeding (20). A high rate (96%) of exclusive breast feeding in this study was the result of the government's effort in the past few years to promote breast feeding.

This analysis also revealed no significant trend toward higher rates of resolution in patients with highly educated parents, mode of delivery, consanguinity between parents, father smoking, and age of introduction of solid food.

The limitations of this study include the small sample size of the infants and children, absence of measuring the cow's milk-specific IgE levels at baseline, and follow-up of the infants and children. Atopic dermatitis was considered as a predictive factor, but we could not determine the index of severity of skin symptoms. Prospective studies will be needed to follow all patients for growing out of CMA in longer period.

In conclusion, about one half of the infants and children with IgE-mediated cow's milk allergy developed tolerance by 18 months of follow up. Parental allergy and atopic dermatitis were important predictor factors for the persistence of CMA. Follow-up of CMA patients is important in appropriate timing of re-introduction of cow's milk to the diet.

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