

Prevalence of immediate hypersensitivity reactions to cow's milk in infants based on skin prick test and questionnaire

E. Kucukosmanoglu^a, D. Yazici^b, O. Yesil^b, T. Akkoc^b, M. Gezer^c, C. Özdemir^b, N. Bakirci^d, N.N. Bahceciler^b and I.B. Barlan^b

^aGaziantep University Medical Faculty. Department of Pediatrics. Gaziantep. Turkey. ^bMarmara University Medical Faculty. Division of Pediatric Allergy and Immunology. Istanbul. Turkey. ^cOkmeydani Teaching Hospital. Department of Pediatrics. Istanbul. Turkey. ^dMarmara University Medical Faculty. Department of Public Health. Istanbul. Turkey.

ABSTRACT

Objective: Cow's milk (CM) hypersensitivity is one of the most frequent hypersensitivities in infants. The objective of our study was to investigate the prevalence of immediate hypersensitivity to CM based on skin prick test results and to evaluate associated allergic conditions ascertained by questionnaire in infants living in Istanbul.

Methods: All infants born between June 2001 and May 2002 were recalled to the hospital according to their dates of birth, and 1015 infants aged between 8-18 months were included in the study. An interview was conducted with each mother and a questionnaire requesting data on cow's milk hypersensitivity and other allergic diseases was completed during this interview. A cow's milk skin prick test (SPT) was applied to all infants. An open CM challenge test was then carried out on infants with a positive SPT to CM.

Results: Among the 1015 infants who underwent SPT, six (0.59 %) demonstrated immediate hypersensitivity to the CM allergen and three (0.29 %) developed a positive response to the CM challenge test. The results of the questionnaire revealed that 112 (11.0 %) of the infants had family history of allergic diseases, 96 infants (9.5 %) had a positive history of recurrent wheezing, and 166 (16.4 %) had a history of skin rash resembling atopic dermatitis.

Conclusions: Our results suggest that CM hypersensitivity, with its low prevalence, might not be a serious health concern in Turkish infants.

Key words: Immediate hypersensitivity. Cow's milk allergy. Skin prick test. Allergic diseases. Infant.

INTRODUCTION

The prevalence of food allergy is high during the first years of life, affecting about 6 % of infants under 3 years of age¹. As the first protein to be introduced into an infant's diet, cow's milk (CM) is the most common allergen to be implicated in food allergies during infancy. Epidemiological studies indicate that about 1.9 % to 7.5 % of infants experience hypersensitivity reactions to CM during the first year of life^{2,3}. While the majority of infants outgrow their cow's milk allergy (CMA) by the third year of life, 15 % retain their sensitivity into the second decade⁴.

Correspondence:

Ercan Kucukosmanoglu, MD
Gaziantep Universitesi Tip Fakultesi
Pediatri Anabilim Dalı
Universite bulvarı 27310
Gaziantep-Turkey
E-mail: ercankosmanoglu@yahoo.com
ercankosmanoglu@hotmail.com

Many studies have shown that avoidance of CM in infants that are at risk of developing atopic diseases lowers the occurrence of allergic diseases due to CM⁵⁻⁸. Many nutrition guidelines in developed countries suggest avoidance of introduction of whole CM as a drink until 12 months of age, whereas Denmark, Sweden and Canada permit introduction of CM at the age of 9-10 months of age.⁹

In our country, CM is widely used for the nourishment of infants under 1 year of age¹⁰. It is also important to determine the prevalence of CMA in Turkey so that appropriate recommendations can be given regarding complementary feeding. The number of studies evaluating the prevalence of CMA among the Turkish infants is limited. A study by Altintas et al¹¹ found a total cumulative prevalence of 1.55 % in the first two years of life, suggesting that the frequency of CMA among infants may be less than the rates reported in other European countries^{2,3}. The objective of our study was to investigate the prevalence of immediate hypersensitivity to CM in infants between the ages of 8-18 months living in Istanbul.

METHODS

Study Population

The study was conducted at Okmeydani Hospital between October 2002 and January 2003 as a hospital-based cross-sectional study without long-term follow-up of the included children. All infants who were born at the same hospital between June 2001 and May 2002, with an age range of 8 to 18 months, were invited for participation in the study. The formation of the study population consisted primarily of families of workers. Participants were recruited according to their birth order. Upon the phone invitation, 1015 infants out of 1415 (71.7 %), who were born in this time period, attended the hospital. Three hundred infants could not be reached. Eventually, 1015 infants were included in the study. The study protocol was approved by Marmara University Hospital Ethics Committee. All parents were informed about the study and signed consents were obtained.

Study Design

Questionnaire

A face-to-face interview was conducted by one of the authors with each mother and a questionnaire seeking data on CMA and other allergic diseases was completed at the same time. The presence of

a history of wheezing, atopic dermatitis, breastfeeding, age of initiation of complementary food, CM intake, and family history of atopic diseases were queried and recorded in detail according to the questionnaire.

Skin Prick Test

Skin prick test (SPT) was performed in duplicate with a lancet with 1 mm tip (Mizollen) on the volar surface of the forearm. Standardised allergen extracts from whole CM extract (Hollister-Stier Laboratories, USA) were employed. Histamine dihydrochloride (10 mg/ml) and diluent served as a positive and negative control, respectively. Skin response was measured 15 minutes later, considering a wheal diameter of 3 mm or larger as a positive skin reaction to the diluent¹².

Laboratory Studies

Furthermore, CM-specific IgE levels were determined in subjects with a positive SPT by using the Pharmacia CAP system FEIA (Pharmacia, Uppsala, Sweden).

Open Food Challenge Protocol

Infants with a positive SPT to CM were put on an elimination diet two weeks prior to the oral challenge test. CM and related products containing dairy proteins were excluded from the infant's diet. All previously prescribed antihistaminic medications were restrained from use. Challenge was performed under hospital settings starting with 2 ml of CM, which was then increased in volume every 30 minutes (followed by 5, 10, 20, 50, 100 ml) until the final dose of 100 ml was ingested. All patients were examined prior to and during the challenge for the presence of any allergic reaction. The challenge was terminated when objective symptoms were noted by the study physician. Infants were also observed for a minimum of 4 hours in the hospital settings or until signs of clinical reactivity subsided for those patients who failed the challenge test. After completion of the test, parents were instructed to continue giving 100 ml of CM daily for the following 7 days. All parents were informed about late-phase reactions before discharge from the hospital and instructed to contact the supervising physician in case of any reaction. At the end of the 7th day, infants were re-examined.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) program (Release 11.0; SPSS Inc. Chicago, Illinois, USA). Data were obtained as descriptive statistics.

RESULTS

Among 1415 infants born between June 2001 and May 2002, parents of 1015 infants who could be reached (female/male 490/525, mean \pm SD age: 12.5 \pm 2.5 months) agreed to participate in the study. The participation rate in the study was 71.7 %. Demographic characteristics of the study population are presented in Table I. Of the 510 infants of less than one year of age, 442 (86.7 %) had CM in their daily nutrition composition and the mean consumption of CM was 342 ml (Table I). The results of the question-

Table I
Demographic characteristics of the study group
(n = 1015)

	Mean	Median	(range)
Age (months)	12.49	12.00	(8-18)
Birth weight (g)	3344.12	3350	(1000-5000)
Weight (g)	9571.0	9500	(6000-15750)
Age (months) at initiation of complementary foods	4.12	4.00	(1-13)
Age (months) at initiation of cow's milk	6.40	6.00	(1-15)
Daily ingestion cow's milk (ml)	339.10	300	50-1200
Age < 12 months (n = 510)	342.19	250	50-1000
Age > 12 months (n = 505)	337.33	300	50-1200

Table II
Clinical features of infants in relation to cow milk hypersensitivity (n = 1015)

Allergic disease in family	112 (11.0 %)
Allergic disease in mother	46 (4.5 %)
Allergic disease in siblings	44 (4.3 %)
Allergic disease in father	27 (2.7 %)
Recurrent wheezing	96 (9.2 %)
History of skin rash resembling atopic dermatitis	166 (16.4 %)
Breastfed infants since birth	966 (95.2 %)
Cow-milk fed infants (alone or in addition to breastfeeding)	908 (89.5 %)
Infants still breastfed at the end of the 6th month	774 (76.2 %)
Formula-fed infants (alone or in addition to breastfeeding)	383 (37.7 %)

naire revealed that 112 (11.0 %) of the infants had family history of allergic diseases, 96 infants (9.5 %) had a positive history of recurrent wheezing, and 166 (16.4 %) had a history of skin rash resembling atopic dermatitis (Table II).

Out of 166 infants, who had a history of skin rash resembling atopic dermatitis, three infants showed hypersensitivity to CM determined by the SPT (1.8 %). Three infants out of 849, who did not have a history of skin rash resembling atopic dermatitis, showed hypersensitivity to CM (0.4 %).

Among 1015 skin prick-tested infants, six demonstrated sensitivity to the CM allergen. CM-specific IgE levels were above the cut-off level in only two of those six infants (CM-specific IgE: 4.09 kU/L and 0.66 kU/L, respectively). Among the six infants who had positive SPT to CM allergen, three (Table III) failed the challenge by developing an urticarial rash during the test and were considered to be positive for the food challenge test. No reaction developed in the other three infants. CM allergy was confirmed by the oral food challenge test in three (0.29 %) infants. No late phase reactions were reported by the families during the 7-day follow-up. Physical examinations of all six infants were normal on the 7th post-challenge day.

DISCUSSION

In this study, we investigated SPT sensitisation to CM. The SPT was the first preference in the study of food allergy since it is easy to perform, inexpen-

Table III
Characteristics of the three infants with cow's milk allergy

	D.C.	K.E.	I.K.
Age (months)	17	10	9
Gender	Female	Male	Female
Birth weight (g)	3400	3250	4200
Weight (g)	9050	9200	9100
Allergic diseases in family	-	+	-
Allergic diseases in mother	-	+	-
Allergic disease in siblings	-	-	-
Recurrent wheezing	-	-	-
Atopic dermatitis resembling skin rash	-	+	-
Age at initiation of CM (months)	Not given	8	Not given
Age at initiation of complementary foods (months)	6	8	8
Duration of breastfeeding (months)	17	10	9
Cow milk SPT (mm)	5 5	3 3	4 4
Cow milk-specific IgE	-	4.09 kU/L	0.66 kU/L
Open cow milk challenge	+	+	+

sive and results are immediately available; moreover, it is very sensitive for IgE-mediated food allergy¹³. Among the 1015 infants, immediate hypersensitivity to CM was found to be 0.59 % (6/1015). CMA was confirmed by the oral challenge test in just three out of six infants (0.29 %).

Various studies have reported a CMA prevalence of between 1.9 %-7.5 %^{2,3}. Although the frequency of CMA during the first year of life tends to be high, nearly 90 % recover by three years of age¹⁴. A prospective, double-blind placebo-controlled study conducted in the United States showed a prevalence of 5.2 % CMA among children under three years of age¹⁵. Host et al¹⁴ reported the prevalence of CMA as 1.1 % in Danish children younger than 30 months of age. On the other hand, Sanz Ortega¹⁶ reported the prevalence as 0.36 % for the first year of life in Spanish infants. In a study from the south of Turkey, in which infants were followed up until two years of age, the cumulative prevalence of CMA was reported to be 1.55 % (21/1348)¹¹. Our result seems to be lower than the results of other studies and it is the only study performed in our country. However, in our current hospital-based cross-sectional study, the median age of infants was 12 months (8-18 months), the period during which it is reported that CMA disappears in approximately 55 % of affected infants. We can assume that some of the children with CMA were excluded due to the natural course of CMA disappearance, and this may have been a contributory factor in the lower rate compared with the other studies.

It has been shown that exclusive feeding of mother's milk for at least four months is associated with a lower cumulative incidence of CMA until 18 months, and it is thus suggested by the European Academy of Allergology and Clinical Immunology¹⁷. In our study, 95.2 % of infants were started on breastfeeding within 24-48 hours after birth. This percentage is consistent with rates reported in the Turkey Demographic and Health Survey (TDHS) study performed every five years in our country¹⁰. The rates of infants initiated on breastfeeding at birth and still breastfed at six months (76.2 %) are higher than in most European countries¹⁸⁻²⁰. This high rate of breastfeeding might be one reason for the low frequency of CM hypersensitivity in our study. Another reason for this low hypersensitivity rate to CM in our study might be due to high daily consumption of yoghurt compared to milk in our country²¹. Mothers consume more yoghurt than milk. It is shown that allergic diseases occur less in people consuming more yoghurt than milk, both in children and adults²²⁻²⁵. In addition, the prevalence of allergic diseases is lower in our country compared to Western countries²⁶.

According to ESPGHAN guidelines, CM should be avoided in infants before 12 months and if necessary, small volumes might be added to the diet. In our study, 86.7 % of the infants were consuming CM before the age of one year. The mean CM consumption was 342 ml. The most common means of giving CM to infants in our country is by cooking CM with rice flour, which is traditionally prepared. It is less expensive compared to regular formulas. Almost all the infants in our study group were from the families whose salary was the minimum wage.

In the present study, when infants were grouped according to the history of skin rash resembling atopic dermatitis, 166 infants (16.4 %) had a positive history of skin rash. Three infants in this group (1.8 %) showed hypersensitivity to CM determined by the SPT, while three infants out of 849 (0.4 %) infants without a history of atopic dermatitis showed positive reaction to CM. A study by EPAAC²⁷ found that 50 % of the infants with atopic eczema between the age of 1 and 2 had hypersensitivity to egg, peanut, house dust mite or grass in cohort. One distinction between the EPAAC study and our study is that regarding atopic dermatitis we depended on the history given by the mothers, while the diagnosis of atopic dermatitis was made by the physicians in the EPAAC study. The low frequency of CM hypersensitivity in infants with a history of skin rash resembling atopic dermatitis might be due to a wrong interpretation of skin rash by the mothers.

In conclusion, we found that the prevalence of immediate hypersensitivity to CM among our population was 0.59 %. The prevalence of CMA confirmed by the oral challenge test was 0.29 %. Our results suggest that CM hypersensitivity might not be a serious health concern in Turkish infants.

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