

# The Predictive Value of Specific Immunoglobulin E on the Outcome of Milk Allergy

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**ABSTRACT:** **Background:** Cow's milk allergy is the most prevalent food hypersensitivity, affecting 2–3% of infants, but it tends to resolve with age. Cow's milk-specific immunoglobulin E in the serum is an important measure in the diagnosis and follow-up of infants and children with cow's milk allergy. **Objectives:** To examine the relation between CmsIgE and the probability of resolution of milk allergy.

**Methods:** CmsIgE was determined in the serum of 1800 infants and children referred for the evaluation of possible milk allergy. All children with CmsIgE of 1 kU/L or above were followed at the allergy clinic and, according to their condition, underwent milk challenge. The diagnosis of cow's milk allergy was made on the basis of a significant and specific history or a positive oral food challenge. Subsequently, oral tolerance was defined as an uneventful oral challenge.

**Results:** A total of 135 infants and children had milk-specific IgE greater than 1 kU/L. Forty-one percent of children still had clinical milk allergy after the age of 3 years. Sixty-eight percent of children older than 3 years with persistence of cow's milk allergy had milk-specific IgE > 3 IU/ml before the age of 1 year. Furthermore, 70% of children who at 3 years old had resolved their cow's milk allergy had milk-specific IgE that was lower than 3 IU/ml before the age of 1 year. The positive predictive value of CmsIgE > 3 IU/ml to persistent cow's milk allergy at age 3 years was 82.6% ( $P = 0.001$ ), with a sensitivity of 67.9% and specificity of 70.4%.

**Conclusions:** Milk-specific IgE concentration in the first year of life can serve as a predictor of the persistence of milk allergy.

**KEY WORDS:** milk allergy, immunoglobulin E, asthma, atopic dermatitis, food allergy

Cow's milk allergy is the most prevalent of all food allergies and affects 2–3% of infants worldwide. Immunoglobulin E-mediated cow's milk allergy tends in most cases to disappear with age [1,2]. The sooner tolerance is ascertained the earlier children can enjoy a

normal and unrestricted diet. This has substantial importance for the normal growth and development of infants and children and in alleviating the emotional burden of their families.

Oral food challenge is the gold standard for the diagnosis of clinical food allergy and is also crucial in determining whether the allergy has been resolved. Advising the parents of children with known food allergy when to perform a repeat challenge is a critical step in the follow-up of these children. Determination of food-specific IgE levels in the serum has proved helpful, but the exact cutoff levels are still a matter of debate. Yet, milk-specific IgE is one of the most important measures in the diagnosis and in the follow-up of infants and children with food allergy [3–7]. Children with a history of food allergy are also at greater risk of having other atopic diseases, including asthma and rhinitis [8]. The aim of the present study was to examine the relation between milk-specific IgE levels in the serum and the probability of resolution of milk allergy, as well as the effect of other allergic conditions on the development of such tolerance.

## SUBJECTS AND METHODS

All tests performed for milk-specific IgE between the years 1994 and 2006 at the immunology laboratory of HaEmek Medical Center for children suspected of having cow's milk allergy were seen by the pediatric allergy unit staff. The serum samples were sent by the primary physicians in the community for infants and children they suspected might have milk allergy. The laboratory serves as the main immunology laboratory for the northern region of Israel. Milk-specific IgE was assessed by the Immulite enzymelinked immunosorbent assay system and included total milk IgE as well as specific IgE towards the different milk components including alpha-lactalbumin, beta-lactoglobulin, and casein. The detection level for milk-IgE was an IgE level higher than 0.35 kU/L. All children with cow's milk-specific IgE of 1 kU/l or above were brought in, examined, followed at the allergy clinic and, depending on their condition, underwent a challenge test with milk. The cutoff point chosen was 1 kU/L because clinical milk allergy is extremely low at lower levels [2,5]

Data collected included gender, other allergies and atopic conditions, family history of atopy, age at onset of symptoms, age and symptoms with accidental exposures to milk, the reported outcomes when milk was introduced at home, and the outcomes of other food allergies.

The diagnosis of cow's milk allergy was made on the basis of a history of symptoms clearly associated with exposure to milk

CmsIgE = cow's milk-specific immunoglobulin E

or a positive oral food challenge. Oral tolerance was defined as an uneventful oral challenge in the clinic or successful home introduction. The primary outcome of interest was acquisition of oral tolerance. Patients who were not likely to have acquired tolerance, on the basis of either a history of recent reactions or elevated milk-specific IgE levels, typically did not undergo oral challenges but continued follow-up. Diagnoses of other allergic such as atopic dermatitis, asthma and rhinitis were based on history and clinical evaluation.

## STATISTICAL ANALYSIS

Analysis was performed using SPSS version 14. Association between the groups of children with and without clinical milk allergy in relation to age and in comparison to their IgE level and other clinical allergic conditions was performed by chi-square test. Multivariate logistic regression was used to predict clinical sensitivity in relation to age together with odds ratio, relative risk and 95% confidence intervals.

## RESULTS

Milk-specific IgE was determined in the serum of 1800 infants and children aged 0–18 years referred for the evaluation of possible milk allergy by their primary physicians in the community. The majority of children were first referred at less than 1 year of age: Mean age at first evaluation was 10.5 months (range 5 weeks to 11 years). Of these, 135 infants and children had milk-specific IgE greater than 1 kU/L; 89 (66%) were males, 105 (78%) were Jewish and 30 (22%) were Arab, similar to their distribution in the general population in the area. Of the 135 enrolled children, 83 (62%) were over 3 years old and 52 (38%) were under 3 years old when the study was terminated. The relation of elevated milk IgE, age and clinical milk allergy is presented in Table 1. As shown, 42% of children older than 3 years still had clinical milk allergy.

Of the 56 children with persistent clinical milk allergy over the age of 3 years, 38 (68%) had had milk-specific IgE > 3 IU/ml in their first year of life. In 19 (70%) of 27 children who had lost their clinical milk allergy before age 3, milk-specific IgE was < 3 IU/ml at or before the age of 1 year. Thus, milk-specific IgE concentration higher than 3 IU/ml in the first year of life carries a risk ratio of 1.69 (95% confidence level 1.19–2.43) of milk allergy

**Table 1.** Milk allergy in relation to age in infants and children with milk-specific IgE > 1 IU/ml

Age (yrs)	Milk allergy positive	Milk allergy negative	Total
> 3	56 (42%)	27 (20%)	83 (62%)
< 3	41 (30%)	11 (8%)	52 (38%)
Total	97 (72%)	38 (28%)	135 (100%)

**Table 2.** Milk allergy and other conditions

Condition	No. (%)
Urticaria	76 (56)
Atopic dermatitis	69 (51)
Asthma	37 (27)
Gastrointestinal symptoms	31 (23)
Allergic rhinitis	17 (13)
Anaphylaxis	2 (1.5)

**Table 3.** Milk allergy and other allergic phenomena

Condition	Sensitivity (%)	Specificity (%)	P	Odds ratio	Positive predictive value
Other food allergies	26.8	96.3	0.01	1.53	93.8%
Urticaria	76.8	48	0.02	1.47	89.5%
Asthma	30.4	92.6	0.02	1.5	75.4%

at age 3 years and above ( $P = 0.001$ ) compared to milk-specific IgE concentration of less than 3 IU/ml. The positive predictive value was 82.6% ( $P = 0.001$ ). The sensitivity of this level is 67.9% and the specificity 70.4%. Seven (5%) of the 135 children had IgE above 100 IU/ml before 1 year of age, which was, as expected, clinically significant in all and had not resolved by age 3.

We next examined the correlation of milk allergy to other allergic phenomena [Table 2]. Persistent cow's milk allergy above the age of 3 years significantly correlated to the presence of other food allergies, urticaria and asthma, but not to atopic dermatitis ( $P = 0.01$ ,  $P = 0.02$ ,  $P = 0.02$ ,  $P = 0.48$ , respectively) [Table 3]. The positive predictive values were 93.8%, 89.5%, and 75.4%, respectively.

Only two children had anaphylactic reaction to milk, and therefore no statistical correlation could be drawn in relation to anaphylaxis in this study.

## DISCUSSION

The prevalence of milk allergy in industrial countries is 1.9–5.2% in children under the age of 3 years, and tends to resolve with age in most children [9]. The ability to predict the course of milk allergy in a specific child is important for both the parents and the physician and determines the necessity of subjecting the child to repeated tests and oral milk challenges. In this work we tried to analyze whether milk-specific IgE can be helpful in such prediction, by examining if the persistence of milk allergy is related to the initial CMiGE in the first year of life. In addition, we examined the relation of milk-specific IgE concentrations to other allergic phenomena. Food allergy was diagnosed by specific IgE and either a clear convincing history or food challenges.

A poor prognosis for milk allergy has been related to genetic and environmental factors such as male gender, non-Caucasian origin, asthma and smoking at home [10]. In this study we did not find

differences related to gender or to Jewish compared to Arab origin. Milk allergy has been associated with other allergic manifestations, and about 30% of milk-allergic children have atopic dermatitis [11]. The presence of atopic dermatitis does not apparently affect the predictive accuracy of IgE concentrations in relation to the outcome of milk challenges [12]. In this study 51% of children suffered from atopic dermatitis, but there was no correlation to the milk-specific IgE concentration. However, we found a highly significant correlation of CMsIgE level with the presence of additional diagnoses of urticaria and asthma and to other food allergies.

In recent years several studies have examined the possibility of using serial or special serum CMsIgE levels for decreasing or even avoiding the need for the complex oral challenge tests, while keeping the predictive values intact [3,4,6,13]. However, there is no full agreement on the validity of this approach [5]. Our work adds to the current knowledge by showing the predictive value of milk-specific concentrations in children under the age of 1 year on the outcome of milk allergy after the age of 3 years. While our results and those of others show that milk-specific IgE concentrations are a useful predictor of challenge outcome in patients with milk allergy [12] as a group, challenge tests under specialist medical supervision are still necessary, because the sensitivity and specificity of milk-specific IgE do not yet allow unequivocal prediction in individual cases

## CONCLUSIONS

Milk-specific IgE concentration in the first year of life can serve as a predictor of the persistence of milk allergy in children. However, their predictive value is such that oral challenges, safely performed by an allergy specialist, remain the gold standard in the diagnosis of food allergy and food allergy resolution.

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