

The natural history of cow's milk allergy in north-eastern Poland

Kaczmarek M*, Wasilewska J, Cudowska B, Semeniuk J, Klukowski M, Matuszewska E

Department of Pediatrics, Gastroenterology and Allergology, Medical University of Białystok, Białystok, Poland

* CORRESPONDING AUTHOR:

Department of Pediatrics, Gastroenterology and Allergology,
Medical University of Białystok
17 J. Waszyngtona,
15-274 Białystok, Poland
Tel: +48 85 74 50 710;
Fax: +48 85 74 23 841
e-mail: maciej.kaczmarek@umb.edu.pl (Maciej Kaczmarek)

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ABSTRACT

Purpose: The rate of cow's milk allergy diminishes with age. There is not enough information concerning geographical trends in persistent cow's milk allergy in children. The objective of the study was to evaluate the prevalence of persistent cow's milk allergy in children previously diagnosed with IgE-mediated cow's milk allergy (CMA).

Material/Methods: Diagnosis of cow's milk allergy was established by a medical history of symptoms associated with exposure to cow's milk, positive skin prick tests with cow's milk, the presence of milk-specific IgE, and by a positive double- or single-blind placebo-controlled food challenge with milk confirmed by a positive open-controlled milk challenge. A second oral challenge was performed after at least one year of a milk-free diet and children with a positive oral milk rechallenge were diagnosed as having a persistent CMA.

Results: Two hundred ninety-one children, 2-14 years of age (mean 5.30±3.16 years, 95% CI, 5.02-5.62 years) completed the study. Persistent CMA was diagnosed in 79 patients (27.1%). Two hundred twelve children (72.9%) outgrew their allergy to cow's milk at a mean age of 5 years after an average time of 16.4±0.8 months on an elimination diet. Eighty percent of children below 3 years of age became milk tolerant. Milk-specific IgE ($p=0.018$) and history of paternal bronchial asthma and/or rhinitis ($p=0.020$) were associated with persistence of cow's milk allergy in regression analysis.

Conclusions: An age above 3 years, as well as features of atopy, individual and familial, may be associated with a risk of delayed tolerance to milk in children.

Key words: cow's milk allergy, milk tolerance, oral food challenge, children

INTRODUCTION

Milk is the first human food and milk's proteins are the first proteins responsible for potentially adverse allergic reactions produced after food intake during early childhood. According to recent guidelines cow's milk allergy (CMA) is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to cow's milk [1]. Milk

allergy is a class 1 food allergy which is characterized by an allergic reaction to foods while they are being ingested, in contrast to class 2 food allergies which are typically the result of sensitization to labile proteins encountered through the respiratory route [2]. The prevalence of cow's milk allergy is estimated to be between 0.5% and 5.2% in children under the age of 3 years with peaks during the first year of life [3-5].

The rates of CMA, in line with other food allergies, seem to be on the increase [6].

Milk induced allergic disorders result from immunologic pathways that include activation of effector cells through food-specific IgE antibodies, cell-mediated reactions resulting in subacute or chronic inflammation, or a combination of the above [1]. Immune reactivity to cow's milk protein (CMP) diminishes with age and clinical tolerance commonly occurs [7]. Oral tolerance to milk is a state of local and systemic immune unresponsiveness to ingested milk that is induced by oral administration of cow's milk proteins (which are innocuous antigens) [8]. Immunologic mechanisms involved in oral tolerance induction include various antigen presenting cells, regulatory T cells, dendritic cells, and most importantly intestinal epithelial cells [9]. It is suggested that by the age of 3 years, 85% of children will have regained tolerance to CMP [10]. According to other authors, CMA may persist in 13%-49% of children until the age of 3 [10, 11].

Clinical phenotypes of persistent CMA are varied and involve one or more target organs with the main targets being the skin, respiratory system, and gastrointestinal tract. Multi-organ involvement and IgE-mediated mechanisms are the main predictors of persistence of CMA. The diagnosis of CMA includes taking a medical history, skin tests, immunological laboratory studies, and additionally requires cow's milk elimination from the diet followed by a challenge test. The only reliable way to diagnose CMA is by a double-blind, placebo-controlled challenge [12]. If the result of the blinded challenge is negative then confirmation by means of an open and supervised feeding of a typical serving of the food to rule out a false-negative result is required [2]. Persistence of CMA manifests both clinically and in laboratory results after re-introduction of milk [13].

'Diagnosis and Rationale for Action against Cow's Milk Allergy' (DRACMA, 2010), published by the World Allergy Organization, has underlined that there is not enough information concerning geographical trends in cow's milk allergy in children from challenge – based studies [6]. There is not enough information concerning persistent cow's milk allergy and there are also no sufficient studies from Poland. This study was designed to evaluate the prevalence of persistent cow's milk allergy based on oral milk challenges. The main outcome measure was the number of children whose clinical symptoms, previously recorded after a controlled exposure to cow's milk, subsided or discontinued. A follow-up was performed after a period of avoidance (cow's-milk-free diet) to assess the progression of clinical symptoms of CMA. The study population was recruited from a region of Poland characterized by a high production and consumption of cow's milk.

MATERIALS AND METHODS

Participants and study design

This prospective, non-randomized study included children diagnosed with cow's milk allergy. Children diagnosed in the Department of Pediatrics, Gastroenterology and Allergology of the Medical University of Białystok between September 2004 and November 2009 were recruited. The patients ranged in age from 2 to 14 years. The diagnosis of cow's milk allergy was established by the following criteria: medical history of symptoms associated with exposure to cow's milk, positive skin prick test (wheal diameter \geq 3 mm) with cow's milk allergens and/or the presence of milk-specific IgE (>0.7 kU/L was taken as the lower limit) against definite components of cow's milk proteins (casein, alpha-lactalbumin, beta-lactoglobulin), and by a positive double- or single-blind placebo-controlled food challenge with milk (D/SBPCFC) confirmed by a positive open-controlled milk challenge [14-16]. Children with a positive oral milk re-challenge were diagnosed as having a persistent CMA and clinical symptoms recorded after milk re-introduction were submitted for analysis. This study protocol followed ethical guidelines and was approved by the Bioethics Committee of the Medical University of Białystok.

Data collected included any family history of atopy (only physician documented data were included), individual history of feeding (i.e. breastfeeding, first exposure to allergens such as egg and wheat), any history of allergic disease (i.e. skin-onset or gastrointestinal-onset of disease), and any current diagnosis of allergic disease. The diagnosis of atopic dermatitis was based on the criteria by Hanifin and Lobitz which include pruritus, a typical morphology of facial and extensor involvement, and a tendency to chronic or chronically relapsing dermatitis [17]. The activity of the disease process was evaluated based on the SCORAD index (SCORing Atopic Dermatitis), which takes into account the topography, severity of skin lesions, and subjective symptoms (itching, sleep disturbances) [18].

Inclusion criteria of the second oral cow's milk challenge were: 1. negative history of infection in the last two weeks before the challenge; 2. stable phase of allergic disease (child did not need systemic pharmacological treatment); 3. at least one year of treatment with a cow's milk-free diet.

Exclusion criteria were: 1. lack of parent's consent (four patients had a past history of anaphylactic reaction); 2. signs or symptoms of any infection within two weeks prior to the challenge; 3. exacerbation of allergic symptoms and a need for medication; 4. lack of strict adherence to dietary recommendations.

Assessment of sensitization to cow's milk proteins

Sensitization to cow's milk protein was assessed by a skin prick test with cow's milk and a measurement of specific IgE levels in the serum. Skin tests with food allergens and aeroallergens were made according to the European Academy of Allergy and Clinical Immunology recommendations [19].

Skin tests with native fresh foods were performed using the prick-by-prick technique. A drop of fresh cow's milk and other fresh foods were placed on the volar side of the forearm and pricked with a 19 gauge lancet. Skin tests with commercial aeroallergens (Allergopharma, Germany) were performed and 9% codeine was used as a positive control and 0.9% NaCl as a negative control. Skin reactions were assessed after 15 minutes. A wheal diameter equal to or greater than 3 mm or more than half the average diameter of the positive controls was considered to be positive in the presence of a negative control.

Blood samples (2 ml) were collected between 8 - 9 a.m. before the start of the oral cow's milk challenge and sera were stored at -20 C until analysis. A UniCAP automatic analyzer (Pharmacia, Sweden) was used for the measurement of total IgE, as well as IgE specific to cow's milk, alpha-lactalbumin, beta-lactoglobulin, and casein in the serum of patients. The detection limit of the CAP system is 0.35 kU/L IgE; measurable specific IgE was defined as a positive test result if values were >0.7 kU/L.

Cow's milk challenge procedure.

The cow's milk challenge was performed according to recommendations by the European Academy of Allergy and Clinical Immunology [20]. The first and second oral cow's milk challenges were carried out using the same procedure in our clinic which was equipped and staffed to undertake any emergency interventions. The challenge protocol was preceded by four weeks of diet monitoring in a journal in order to assess if the child's diet was truly cow's milk-free and hypoallergenic (elimination of eggs, peanuts, cocoa, fish, soya, and artificial dyes was recommended). Any medications and symptoms were recorded to assess if the patient's condition was stable and if discontinuing antihistamines did not result in an exacerbation of allergic symptoms. Also, parents were recommended to avoid giving nutritional supplements and herbs. All the parents were instructed on how to observe and record symptoms. Signs and symptoms were monitored before the challenge (i.e. during the elimination diet), during the challenge, and up to 28 days thereafter. Parents were in constant phone contact with the medical team of the study and all problems by phone were noted in the patients' medical documentation.

The challenge was started with a labial milk challenge (LMC) using the technique described by Moneret-Vautrin *et al.* [21]. If no significant reaction was observed, the oral milk challenge was started. A low-lactose cow's milk formula containing a small amount of lactose (< 0.01 g%) was used

as the verum with an amino acid formula as a placebo. A drop of cow's milk was put upon the inner border of the lower lip. If no adverse reactions occurred within 15 min., increasing doses of milk (1.0, 15, 50, and 100 ml) were given at 30 min. intervals. Vital signs (pulse rate, blood pressure, and, in older children, peak flow meter) were recorded before and after each verum/placebo administration. After the last CM administration the children were observed for at least 4 more hours also with observations being performed at 30 min. intervals. Patients were then discharged. The test was terminated if any symptoms were observed during the challenge. If no immediate, anaphylactic reaction occurred, the challenge was continued at home with a daily 100 ml dose of milk for 28 consecutive days. This period served to rule out any late-onset reactions caused by cow's milk. A last visit after these 4 weeks confirmed if the child fully recovered and was freely tolerant of dairy products.

A challenge was considered as *positive* if an allergic reaction involved digestive (vomiting, diarrhea, lip swelling), cutaneous (urticaria, exacerbation of eczema, angioedema, rash), respiratory (stridor, coughing, asthma/wheezing), nasal (rhinitis/rhinoconjunctivitis), or systemic symptoms/reactions and the result of the placebo challenge was negative. Immediate symptoms were defined as occurring up to 2 hours after the last milk challenge dose. Symptoms occurring between 2 and 48 hours after the last milk challenge dose were defined as late-onset symptoms. Any child with a positive challenge was considered not tolerant to cow's milk protein and to have persistent allergy.

A challenge was considered as *negative* if there was a lack of allergic symptoms following reintroduction of cow's milk during the 28 days post-discharge. Any child with a negative challenge was considered tolerant to cow's milk protein.

Statistical analysis

The Student's t-test was applied to compare variables of a normal distribution, the Mann-Whitney *U*-test to compare variables of non-parametric distribution, and the Shapiro-Wilk test to verify the statistical shape of the tested variable distribution. The Chi-square (χ^2) test for independence and Fisher's exact test were applied to compare the qualitative and categorized variables. Regression analysis was applied to assess the influence of risk factors on the persistence of cow's milk allergy. Statistical significance was defined by a level of 0.05. All data management and statistical analyses were performed with StatSoft (STATISTICA data analysis software system, version 9.0).

RESULTS

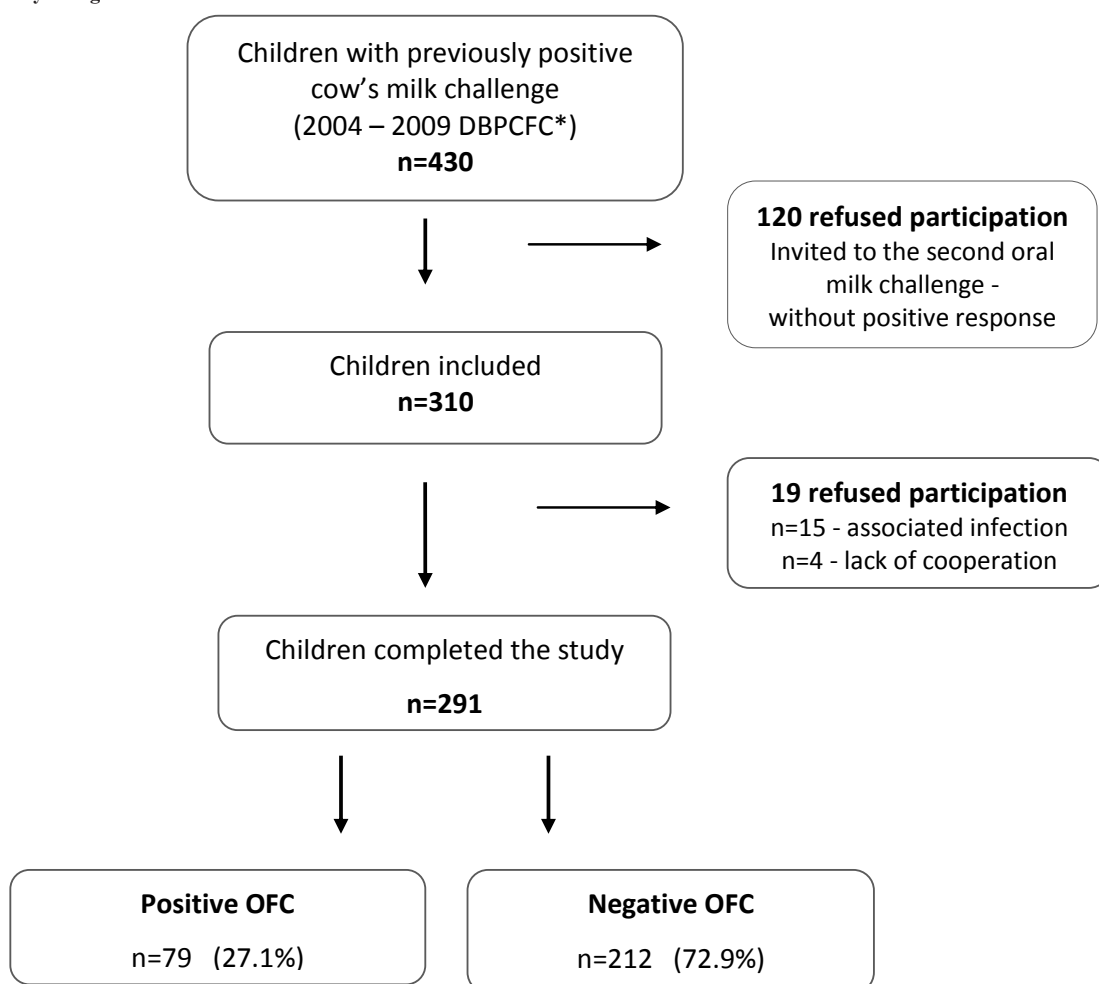
Four hundred and thirty patients diagnosed with cow's milk allergy were invited to the second cow's milk challenge. The parents of 310 children gave written consent for the study. The

parents of 19 patients declined further participation, yielding a drop-out rate of 6.1%, and a feasibility of 93.3%. Due to associated infections, 15 out of 19 patients were withdrawn from the study and 4 of 19 patients were withdrawn because of a lack of adherence to dietetic recommendations (parents failed to institute the appropriate diet in their children) (Fig. 1). Thus, 291 children, 2-14 years of age (mean 5.30 ± 3.16 years, 95% CI, 5.02-5.62 years) completed the study; 128 girls and 163 boys, 43.6% and 56.4% respectively. The duration of a cow's milk-free diet was 16.4 ± 0.8 months (range 1-4 y). Re-introduction of cow's milk in 291 children resulted in 79 patients (27.1%) presenting with positive results of a challenge to cow's milk (Tab. 1). In 212 children (72.9%), an oral provocation test with cow's milk protein was negative and these children were considered to be tolerant to cow's milk. Twelve out of 212 children presented with ambiguous signs and were hospitalized but ultimately negative results in a double-blind challenge were confirmed.

In the subgroup of children <3 years of age the result of the oral cow's milk re-challenge was negative in 80% and positive in 20% of the children (Fig. 2). The percentage of positive results of this challenge was higher in the older age group (3-6 years) and the highest in children >6 years of age, 27.6% and 32.4% respectively. The difference between the first and third group, however, was on the border of statistical significance ($p=0.071$, Fisher's exact test).

Children diagnosed with persistent cow's milk allergy and those with negative milk challenge results did not differ in gender, breastfeeding duration, introduction time of eggs and wheat into their diet, and total serum immunoglobulin E levels (Tab. 1). Prevalence of positive skin prick tests to aeroallergens was comparable in both groups: 15.5% vs. 14.2% respectively ($p=0.622$). Both studied groups differed in status of sensitization to cow's milk protein at the time of diagnosis. Children diagnosed with a persistent cow's milk allergy were characterized by a higher prevalence

Figure 1. Study Design.

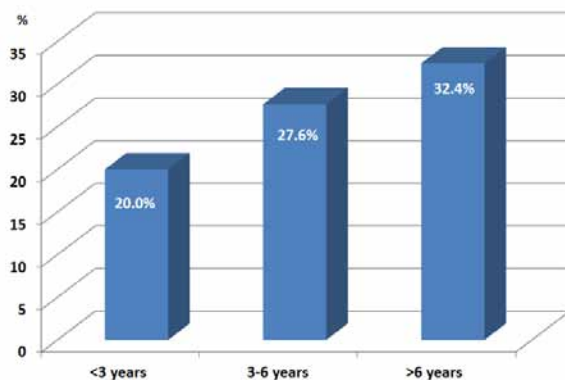


*DBPCFC - Double Blind Placebo Controlled Food Challenge

Table 1. Characteristics of the study population according to sensitization status to cow's milk protein at the time of diagnosis.

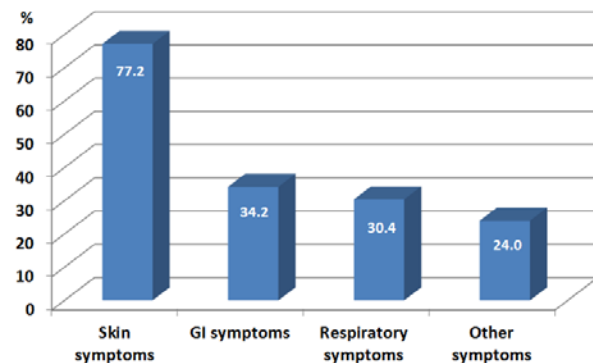
	Milk allergy Positive (No = 79)	Milk allergy Negative (No = 212)	P value
Age, years	4.8 ± 2.6	5.2 ± 2.5	0.213
Age subset			
< 3 y, No	13	52	0.071
3-6 y, No	42	110	
>6 y, No	24	50	
Female, No (%)	41 (51.9)	87 (41.0)	0.097
Breastfeeding duration (months)	7.5 ± 9.5	7.7 ± 7.6	0.877
Total serum IgE (IU/mL) (95% CI)	121.53 ± 306.28 (38.70 - 204.33)	117.31 ± 274.62 (72.07 - 162.54)	0.925
Total IgE > 100 IU/mL, No (%)	15 (19.0)	38 (17.9)	0.834
Positive milk SPT (>= 3mm), No (%)	48 (60.8)	57 (21.4)	0.000
Milk SPT – mean wheal diameter (mm)	3.8	1.2	0.024
Cow's milk IgE > 0.7kU/L, No (%)	53/74 (71.6)	49/203 (24.1)	0.000
Alpha-lactalbumin IgE > 0.7 kU/L, No (%)	13/69 (18.8)	18/191 (9.4)	0.039
Beta-lactoglobulin IgE > 0.7kU/L, No (%)	37/69 (53.6)	27/191 (14.1)	0.000
Casein – IgE (kU/L), No (%)	17/65 (26.2)	41/197 (20.8)	0.368

Data expressed as mean ± standard deviation, CI - confidence interval, SPT – Skin prick test

Figure 2. Distribution of positive cow's milk re-challenge in different age groups.

of positive skin tests with cow's milk than milk tolerant children, 60.8% vs. 24.1% respectively ($p < 0.001$), as well as a higher prevalence of increased level of milk-specific IgE antibodies, particularly to beta-lactoglobulin, 53.6% vs 14.1% respectively ($p < 0.001$) (Tab. 1).

Symptoms elicited during the D/SBPCFCs were as follows: cutaneous 77.2% (n = 61), gastrointestinal 34.2% (n = 27), and respiratory 30.4% (n = 24) (Fig. 3). No generalized anaphylactic reactions were noted during both cow's milk challenges. The most common skin reactions were exacerbations of atopic dermatitis (42/61; 68.9%) and urticaria (23/61; 37.7%). The most common gastrointestinal reactions were abdominal pain (12/27; 44.4%), vomiting or nausea (11/27; 40.7%), diarrhea (7/27; 25.9%), and constipation (5/27; 18.5%). The most common respiratory reactions were cough (11/24; 45.8%) and rhinitis (11/24; 45.8%). A behavioral

Figure 3. Clinical symptoms of cow's milk allergy during positive cow's milk re-challenge.

reaction was observed in 14 (17.7%) children. Five (6.3%) children had a febrile reaction.

Predictors of a positive cow's milk challenge in the studied population were: serum milk-specific IgE > 0.7kU/L ($p = 0.018$), paternal history of atopic disease in the form of bronchial asthma and allergic rhinitis ($p = 0.020$), positive skin prick test with soybean ($p = 0.038$), and skin onset of cow's milk allergy ($p = 0.041$) (Tab. 2).

DISCUSSION

The main finding in our study is that 72.9% of 291 studied children outgrew their allergy to cow's milk at a mean age of 5 years after an average time of 16.4±0.8 months on an elimination diet. We have found that the process of outgrowing

Table 2. Predictors of positive cow's milk re-challenge in univariate regression analyses.

Factor	Crude OR	95% CI	P value	
Sex	0.645	0.38-1.09	0.098	
Breastfeeding duration	1.002	0.97-1.03	0.877	
First exposure to chicken egg	1.285	0.99-1.69	0.070	
First exposure to wheat	0.997	0.63-1.56	0.990	
Gastrointestinal - onset	1.337	0.72-2.49	0.358	
Skin - onset	2.219	1.03-4.79	0.041	
Milk-specific IgE (> 0.7 kU/L)	2.352	1.12 -4.62	0.018	
Positive skin prick test - any food	1.251	0.61-2.54	0.532	
Positive skin prick test - soybean	2.384	1.04-5.45	0.038	
Positive skin prick test - any aeroallergen	0.933	0.68-1.28	0.665	
Family history of atopic diseases	1.914	1.06-3.46	0.031	
	Mother	0.884	0.46-1.70	0.713
	Father	2.261	1.13-4.52	0.020
	Siblings	1.782	0.99-3.18	0.049

OR - odds ratio; CI - confidence interval

the milk allergy tended to be faster in the youngest children below 3 years of age as confirmed by negative challenge tests in 80% of the children. In older age subgroups the percentage of patients who developed tolerance to milk was lower being 72.4 % for children 3-6 years and 67.6% for children > 6 years.

This is the first clinical challenge-based study on cow's milk tolerance in Poland. All of the studied children were residents of north-eastern Poland, a region characterized by high milk production and consumption (ranked 2nd among the 16 provinces in 2009, 17.6% of total domestic milk production, <http://www.stat.gov.pl/>). As the study subjects were recruited from a population with a high exposure to milk this may have resulted in a higher risk of milk sensitization. However, results of our study are comparable with those described by other authors [10, 22, 23]. According to Sicherer *et al.* [22], approximately 85% of children lose their sensitivity to most allergenic foods (milk, eggs, wheat, and soya) within the first 3-5 years of life. A high recovery rate was also reported by Host and Haller, who, in a community-based series, found that up to 87% of children with CMA in infancy achieved tolerance by the age of 3 years [10].

An important finding in our study is that the father's respiratory phenotype of atopy was a predictor of a persistent milk allergy in the child. Paternal bronchial asthma and/or rhinitis were associated with a child's positive cow's milk re-challenge. It is known that epidemiological risk factors for persistent cow's milk allergy include an association with atopy. A link between cow's milk allergy and bronchial function has been studied previously [4, 24, 25]. In a study by Zeiger and Heller, paternal asthma was also a significant predictor of a child's food sensitization [24]. It is suggested that cow's milk allergy may precede respiratory allergy. In

a study by Malmberg *et al.* [26], cow's milk allergy in early childhood was a significant prognostic factor of bronchial asthma in later childhood. Bronchial hyperresponsiveness to histamine and airway inflammation expressed as higher levels of exhaled nitric oxide was found by the authors in school age children with a history of IgE-mediated cow's milk allergy. A prospective follow-up is needed to record respiratory symptoms in children with persistent cow's milk allergy in our study, especially those with a history of parental asthma.

Milk-specific IgE, a marker of atopy, was previously described as a strong predictor of the persistence of cow's milk allergy [4]. In our study a high prevalence of IgE-mediated CMA (71.6%) in the group with a positive cow's milk challenge confirms that the natural outcome of CMA depends on the status of milk-specific IgE [26]. In a study by Vanto *et al.* [11] with Finnish children, all of the children with non-IgE-mediated allergies became tolerant to cow's milk by the age of 3, as compared to only 71% infants with IgE antibodies. Similarly, Hill *et al.* [27] reported a low rate of remission in children at the age of 3 with IgE-mediated allergies compared with non-IgE mediated allergies (37% vs. 78%). Also, according to Host *et al.* [10], tolerance is acquired more rapidly by children with symptoms mediated by non-IgE mechanisms in comparison to children with IgE-mediated cow's milk allergy.

A higher prevalence of increased serum sIgE to alpha-lactalbumin and beta-lactoglobulin, but not for casein, was found in the group with persistent CMA. In previous studies, children with clinical cow's milk allergy had greater skin prick test reactivity than tolerant control individuals for whole-milk, alpha-lactalbumin, and beta-lactoglobulin, but not for casein [28]. In a recent study it has been suggested that

oral tolerance is associated simultaneously with decreasing CMP-specific IgE and increasing IgG4 production [25, 29, 30]. The cut-off levels of sIgE in the diagnosis of cow's milk allergy are still a matter of debate. It should be mentioned that serum milk-specific IgE reflects allergic sensitization and not necessarily clinical allergy. According to Sampson [31], undetectable serum food-specific IgE levels might be associated with clinical reactions in 10% to 25% of patients with CMA. Therefore, the measurement of milk-specific IgE may be useful but an oral milk challenge is still necessary as a basis for diagnosing a developing tolerance to oral milk and a resolution of allergy.

Children with persistent cow's milk allergy demonstrate multi-organ symptoms affecting mainly the skin, gastrointestinal, or respiratory tracts [10, 16, 32]. In this study, skin symptoms, mainly atopic dermatitis, were most common in patients diagnosed with persistent cow's milk allergy. Cow's milk as well as other food allergens can induce urticarial lesions, itching, and eczematous flares, all of which may aggravate atopic dermatitis (AD) [33]. Skin and gut integrity may play a role in food-associated skin symptoms. Recent genetic studies have demonstrated that filaggrin gene mutations play a critical role in reduced skin barrier function, enhanced cutaneous allergen absorption, and systemic allergen sensitization [34]. Furthermore, the structural integrity of the gut barrier depends on epithelial junction complexes and tight junctions. According to an observation by De Benedetto et al. [35, 36], reduced expression of the tight junction claudin in the skin of patients with AD is of particular interest given the association of AD with food allergy. Gastrointestinal symptoms in the studied children were isolated or combined with skin or respiratory symptoms. Rare clinical manifestations of cow's milk allergy in the form of behavioral or psychomotor disturbances were observed in a few patients after exposure to cow's milk. Also, milk-induced fever, a relatively rare symptom of allergy [37], was observed in five patients. All episodes of fever developed within 48 hours following commencement of the provocations and did subside directly after milk withdrawal. Fever, due to food allergy, is rarely taken into account and as such is easily overlooked [37-40]. Therefore, we suggest that body temperature could be considered in the list of symptoms routinely monitored during a food challenge.

The presence of other food allergies is a factor predisposing to persistent milk allergy after 3 years of age [41]. In our study, sensitization to soybean was a predictor for persistent CMA. Soy allergy occurs in only a small minority of young children with IgE-associated CMA [42]. Therefore, a suggested, but not confirmed, explanation of our finding is that cow's milk allergy may have resulted from cross-reactivity between a soy protein component and caseins in cow's milk [43].

There are several limitations in this study. One of them is that a relatively high number of children with a positive

challenge result did not complete the study due to parents not continuing with a second challenge. However, this limitation is understandable as it reflects the natural history of cow's milk allergy which is characterized by a spontaneous discontinuation of the allergy. Early discontinuation of a challenge in order to prevent a more generalized allergic reaction may have resulted in a false-positive result. Nonspecific symptoms of allergy such as diarrhea, nausea, vomiting, itching or cough are potential sources of diagnostic error/bias. A false-positive diagnosis could have led to unnecessary dietary restrictions and possible disease due to inadequate nutrient intake [44]. False-negative diagnoses were still possible despite the usage of open challenges to confirm negative blinded challenges. False-negative diagnoses are described as being present in approximately 1% to 3% of challenges and can lead to a risk of ongoing symptoms [1].

CONCLUSIONS

In conclusion, this study investigated the prevalence of persistent cow's milk allergy based on blinded challenges. An age above 3 years, IgE-mediated cow's milk allergy, and a history of atopic diseases represented by paternal bronchial asthma and/or rhinitis were associated with positive re-challenge results with milk. An age below 3 years and lack of features of atopy (individual and/or familial) were associated with acquisition of oral milk tolerance in 80% of studied children. In the studied population, which was characterized by a high exposure to cow's milk, the outgrowing of milk allergy was common. The early assessment of whether milk intake is safe is important for the normal growth and development of such children. However, one must keep in mind the possibility of de novo sensitization to food allergens or various other foodstuffs (such as eggs) in children with a negative milk challenge [45].

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