

Tolerance to heated cow's milk and egg in children with allergy to this food

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Abstract

Introduction: A total of 75% of children allergic to cow's milk protein and 70% of children allergic to egg white show tolerance to processed milk or eggs. At the same time, it was found that these children represent a milder phenotype of allergy and outgrow it faster.

Aim: To evaluate the possibility of acquiring tolerance to heated cow's milk and egg in children with allergy to these food products.

Material and methods: The study included 26 children with IgE-mediated food allergy, aged 2.1-5.7 years. Children studied were selected from 378 children diagnosed at the Department of Paediatric Allergology, Gastroenterology and Nutrition of the Medical University of Lodz and in the Clinic of Allergology at the Maria Konopnicka Memorial University Teaching Hospital No. 4 in Lodz based on suspected food allergy. Oral provocation was carried out for over two consecutive days: the 1st day with heated allergen, the 2nd day with unheated food allergen. Among the test methods, interview and evaluation of total IgE and specific IgE were also used.

Results: Positive allergen provocation with heated allergen was obtained in 8 children (31%), negative in 18 children (69%). Children with negative oral provocation were challenged with unheated food product. A positive result was obtained in 13 children, revealing in this way the children with allergy to the raw product with simultaneous tolerance to the heated product. A negative result of provocation was found in 3 children with a tolerance to both the unprocessed and processed allergen.

Conclusions: Most children with IgE-dependent allergy to cow's milk protein or egg white tolerate the heated products of these proteins. Evaluation of the acquisition of tolerance in children with food allergy, depending on diet, requires further study.

Key words: cow's milk allergy, egg allergy, tolerance.

Introduction

In view of recent research, allergy to food poses a problem of growing importance. This problem is not necessarily supported by epidemiological data on the prevalence of food allergy, which has been estimated to be at the relatively constant level of 2-8% of children worldwide [1, 2], but by the study outcomes indicating the relationship between food allergy and allergic diseases of the skin or the respiratory tract [3-9]. On the other hand, the data on prevalence of atopic dermatitis (AD) or asthma frequently indicate its increasing tendency [10]. Taking into consideration the fact that food allergy is often a baseline for classical progression of allergy we can presume

that by affecting the course of food allergy we can also affect the course of AD or asthma. We do not know whether novel and still improving methods of food allergy treatment or prophylaxis may translate into a decrease in prevalence of other allergic diseases.

To date methods of food allergy treatment have involved the absolute elimination of harmful allergens [11]. Due to the results of observational studies carried out in countries with different prophylactic recommendations for food allergy, which revealed a higher prevalence of allergy to peanuts in cases where their complete elimination had been performed and a lower prevalence in cases where they had been more often applied in the diet, the researchers started thinking whether complete allergen

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elimination is a proper way of management [12-14]. Moreover, it has been shown that tolerance develops when both very high as well as low doses of allergens occur, but not without complete contact with an allergen [15].

Recent studies have suggested the possibility of using another management strategy in food allergy than a strict elimination diet [16, 17]. According to Allen there is no evi-

dence that an incidental intake of food delays the development of tolerance, i.e. incidental episodes of exposure to allergen do not cause a delay in acquiring tolerance to a particular food allergen [18]. What is more, it has not been confirmed that exposure to an allergen during an oral challenge test resulting in an allergic reaction decreases the chance to acquire tolerance. The statement that the elimination of a previously tolerated allergen leads to an allergic reaction after repeated exposure has encouraged researchers to carry out investigations on new trends in food allergy therapy [19]. Moreover, oral immunotherapy has been found to be effective at least in desensitization of children with IgE-dependent allergy [20], and some children with allergy to cow's milk proteins or egg tolerate these allergens in a processed form [21, 22].

Nearly 75% of children with allergy to cow's milk protein and 70% of children with allergy to egg white exhibit tolerance to these allergens in a processed form. Processed allergens are obtained by subjecting these allergen-containing products to high temperature (> 170°C). The best way would be to combine them with a proper base, e.g. flour. Heated allergens change their allergenic properties [23]. At the same time it appeared that children with tolerance to the processed allergens of cow's milk protein and/or egg represent a milder phenotype of allergy and outgrow it more quickly [21].

Aim

The aim of the study was to evaluate the possibility of acquiring tolerance to heated allergens of cow's milk proteins and egg white in children with food allergy.

Material and methods

Twenty-six children with IgE-dependent allergy aged 2.1-5.7 years participated in the study. The children were selected from among 378 children diagnosed at the Department of Paediatric Allergology, Gastroenterology and Nutrition of the Medical University of Lodz and in the Clinic of Allergology at the Maria Konopnicka Memorial University Teaching Hospital No. 4 in Lodz because of the suspicion of allergy to cow's milk protein and/or egg white in the period from January 2005 to November 2009. It was the first stage of the study (Fig. 1).

The eligibility criteria were as follows:

- cause-result relationship between onset of complaint and intake of food containing allergens of cow's milk protein and/or egg white confirmed by the parent/patient,
- asIgE > 0.35 kU/l concentration against cow's milk protein and/or egg white allergens,
- positive effect of elimination diet,
- parent's/patient's consent for participation in the study,
- history of the presence of such symptoms as urticaria, rash, eczematous lesions on the skin, vasomotor oede-

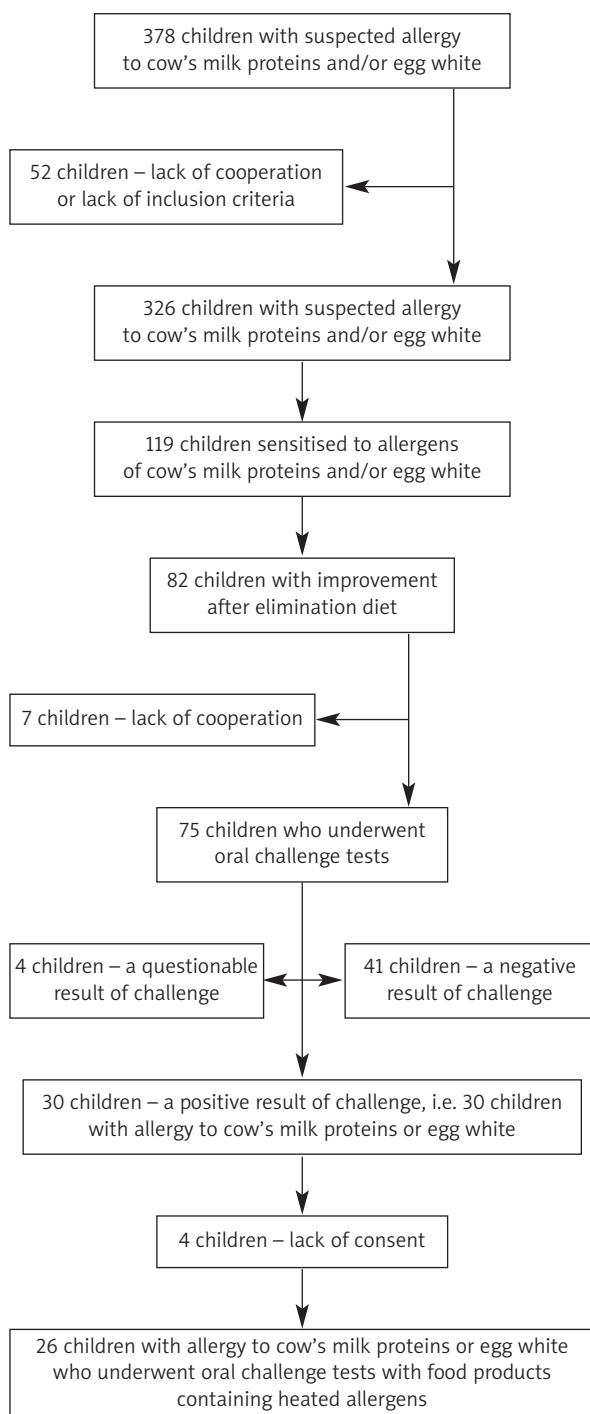


Fig. 1. The first stage examination

ma, itching, vomiting, abdominal pain, diarrhoea, wheezing, cough, breathlessness, rhinitis, shock or fainting after food consumption,

- repeatability of the following symptoms: urticaria, rash, eczematous lesions on the skin, vasomotor oedema, itching, vomiting, abdominal pain, diarrhoea, wheezing, cough, breathlessness, rhinitis, shock or fainting which are associated with the reported food consumption while taking the history.

Exclusion criteria:

- cause-result relationship between onset of complaint and intake of food containing allergens of cow's milk protein and/or egg white, and lack of asIgE > 0.35 kU/l against allergens of these products,
- food allergy to other allergens (including flour) than milk protein and/or egg white allergens,
- concomitant diseases (besides food allergy) which might affect the risk of allergy exacerbation or the course of examination,
- patients in the active phase of disease, i.e. with infection, seasonal allergy, unstable asthma, or with exacerbated AD,
- lactose intolerance,
- medicaments taken such as oral steroids, β -blockers, antihistamines, and inhaled drugs at the time preventing them from performing oral provocation tests.

Due to lack of cooperation or fulfilment of inclusion and exclusion criteria, 52 children were excluded from the study. Based on asIgE concentration in the serum, sensitization to milk or egg allergens was diagnosed in 119 children. An improvement after the elimination diet was observed in 82 children. Seven children were lost; thus 75 children participated in further studies. This group was subjected to an open oral provocation test. A positive result of the test was achieved in 30 children. Among 30 children with food allergy confirmed by the oral provocation test, 14 had allergy to egg white and 16 to milk protein. Four children discontinued participation in the study, so 26 children were classified into the second stage of the research. Six months after diagnosing cow's milk or egg protein allergy, the oral provocation test was performed during two successive days: on the 1st day a heated (processed) allergen was used, selecting in this way the heated allergen-reactive children and those with tolerance to this allergen; on the 2nd day, the heated allergen-tolerant children underwent the provocation test with unheated food allergen, which selected the allergic children and those with tolerance to unheated allergen.

Study methods

- a) A history based on the questionnaire concerned: the type and amount of suspected food, the time between the product ingestion and the onset of symptoms, frequency and type of symptoms (eczema not subsiding after applying emollients, tongue itching, lip swelling, itching, skin erythema or swelling, wheezing, cough,

breathlessness, rhinitis, conjunctival itching and redness, vomiting, diarrhoea, abdominal pain associated with food ingestion), repeatability of symptoms, the time of last ailment appearance after food intake, drugs taken, and possibility of cross-reactions.

- b) tIgE: total serum IgE level was determined by using the electrochemiluminescence method with Roche reagents (Roche Diagnostics, Mannheim).
- c) asIgE: antigen-specific antibodies (asIgE) were determined with the UniCAP 100 method (Pharmacia Diagnostics AB, Uppsala, Sweden) for the following allergens: milk, egg, fish, wheat flour and rye flour, peanut, hazelnut, walnut, soy, cocoa, apple, peach, orange, celery, carrot, potato, and tomato. The level of detection was 0.35 kU/l. Class I: 0.35-0.69 IU/l, class II: 0.7-3.49 IU/l, class III: 3.5-17.49 IU/l, class IV: 17.5-51.9 IU/l, class V: 52-99 IU/l, class VI: > 99 IU/l.
- d) Open oral challenge tests: the trials were carried out according to the EAACI recommendations, after a minimum 2-week elimination diet, in a stable phase of the disease, at least 6 weeks after the last exacerbation, and in an ambulatory setting [24]. The examinations were done by experienced medical and nursing staff. A trained dietician prepared food samples. Native forms of samples were applied, and types of food were based on the patients' medical history and asIgE results. Before application of each sample, administration of antihistamines was discontinued for 2 weeks. Also, inhaled drugs and theophylline were avoided for 48 h prior to the challenge. Systemic glucocorticosteroids (GCs) were contraindicated, while topical GCs for skin lesions were tapered to the minimum dose and kept constant throughout the challenge procedure. The patients were observed for at least 4 h after completion of the final challenge. The food provocation results were scored as negative or positive according to the scale: mild, moderate or severe [25-27]. The patient was asked not to eat anything 2 h before the provocation test. The total dose of the food containing cow's milk or egg allergens was 300 ml and was given every 15 min in 6 portions: 0.2 ml, 0.6 ml, 2 ml, 6 ml, 20 ml, 60 ml, and 200 ml. When the provocation score was negative, a single total food sample containing cow's milk or egg allergens was given on the next day.
- e) Oral challenge tests with heated allergens: oral challenge tests with heated milk protein allergens were performed by using: a cake baked at > 170°C for 30 min containing 1 cup of milk for 1 cup of flour, or waffles baked at 260°C for 3 min. Oral challenge tests with egg allergens were performed by using a cake baked in the proportion of 1 egg to 1 cup of flour. The products were administered every 20 min in equal portions.

Statistical analysis

The statistical analysis was performed using the Mann-Whitney test and Fisher's exact test.

Results

Among 26 children with food allergy, 14 had allergy to cow's milk protein, and 12 to egg white. Table 1 presents the characteristics of the children examined. Atopic dermatitis symptoms were found in 18 children (69.2%). Exacerbation of skin lesions after the oral challenge was observed in 7 of them including 5 children (19.2%) with late reactions and 2 children (7.7%) with mixed reactions. Various types of eczema, e.g. urticarial roseola-like eruption, occurred in 11 children (42.3%), loose stools in 10 (38.5%), vomiting in 5 (19.2%), snuffles in 7 (26.9%), and wheezing in 9 children (34.6%). In 12 children (46.2%) the family history concerning allergic diseases was positive. The symptoms considered as the first manifestation of allergy occurred on average in the 6th month of life; the period of their occurrence ranged from 1 to 24 months. The first symptoms of allergy to milk protein were observed on average in the 3rd month of life, in the case of egg allergy in the 10th month of life. Mean values of tIgE and asIgE levels in the population studied are shown in Table 1.

Twenty-six children with allergy to milk protein and allergy to egg were subjected to the oral challenge test with food containing heated allergens of cow's milk or egg proteins. The schema of the examination is presented in Figure 2. A positive result of provocation was achieved in 8 (31%) and a negative one in 18 children (69%). Among 8 children with allergy to heated allergen, 3 had allergy to egg white and 5 to cow's milk protein, whereas among 18 children with tolerance to heated allergen, there were 9 children in both groups. A strict elimination diet, i.e. avoidance of all foods containing milk or egg protein allergens, was recommended to the children with a positive result of provocation, i.e. with allergy to heated allergen. On the other hand, the children in whom the result of the provocation was negative underwent oral challenge with food containing unheated milk or egg protein allergens, according to the EAACI standards. A positive result of challenge was achieved in 13 children, detecting in this way the children with allergy to unheat-

Table 1. Characteristics of the patients studied

Analysed variable	Children with food allergy
Number	26
Age (mean ± SD) [years]	2.8 ± 2.4 (2.1-5.7)
Sex – boys, n (%)	63
Atopic diseases in the family [%]	46.2
Exclusive breast-feeding for at least 4 months [%]	70
Age of first symptoms appearance – mean months (range)	6.5 (1-24)
tIgE (mean ± SD) [IU/ml]	196.9 ± 142.8
sIgE (mean ± SD) [IU/ml]	7.2 ± 12.6 (0.7-59)

ed allergen and concomitant tolerance to heated allergen. A negative result of provocation was observed in 3 children, which was considered as an effect of tolerance to both unheated and heated allergen. In 2 children the result of provocation was questionable.

In the course of oral positive challenge procedures, the following symptoms were observed: skin lesions (AD exacerbation, etching, roseola-like eruption, urticaria, vasomotor oedema) in 18 children; digestion tract symptoms (abdominal pain, nausea, vomiting, diarrhoea) in 7 children; respiratory symptoms (sneezing, rhinitis, conjunctival reddening and itching, throat irritation, cough) in 14 children; and lower respiratory tract symptoms (wheezing) in 1 child (Table 2). Although allergic symptoms after oral challenge occurred more frequently in the group of heated allergen-reactive children as compared to unheated allergen-reactive children, the differences were not statistically significant ($p > 0.05$).

While classifying the severity of the allergic reactions which were observed following the oral challenge, both children with allergy to heated allergen as well as children with allergy to unheated allergen were found to have a similar severity, most often of moderate intensity ($p > 0.05$) (Table 2).

Mean concentration of asIgE in the group of children with allergy to heated allergen was 13.5 IU/ml (1.3-59 IU/ml), in children with tolerance to heated allergen it was 5.2 IU/ml (0.7-34.2 IU/ml), and in those with tolerance to both heated and unheated allergen it was 1.5 IU/ml (0.2-2.9 IU/ml) (Table 3).

Discussion

Eggs and milk are basic food products in the everyday diet of a child. At the same time allergens contained

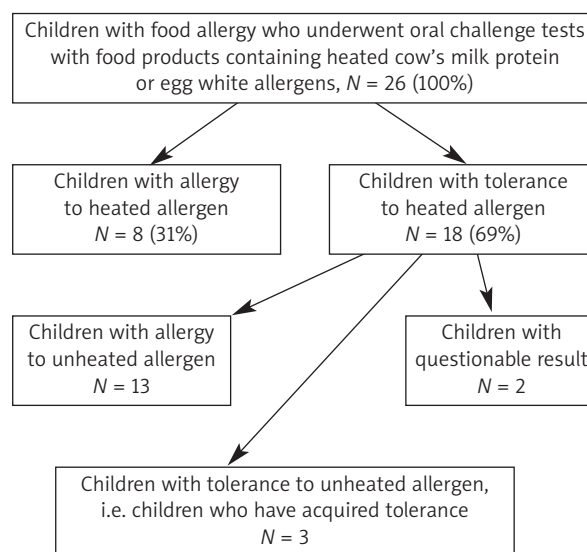


Fig. 2. The second stage examination

Table 2. Symptoms after oral challenge tests in heated allergen-reactive and unheated allergen-reactive children

	Heated allergen-reactive children	Unheated allergen-reactive children	Value of <i>p</i>
Number (%)	8 (31)	13 (50)	
Severity of symptoms mean (range)	2 (1-3)	2 (1-3)	> 0.05
Symptoms during the challenge test (%)			
Skin	7 (87.5)	11 (84.6)	> 0.05
UA	6 (75)	8 (61.5)	> 0.05
LA	1 (12.5)	0	> 0.05
AT	3 (37.5)	4 (30.7)	> 0.05

UA – upper airway, LA – lower airway, AT – alimentary tract

in them are the most frequent cause of food allergies occurring in children. The majority of children with allergy to cow's milk protein and egg white acquire tolerance with time: so about 50% of children with egg allergy acquire tolerance during 3 years and approximately 66% within 5 years [28, 29]. A total of 71% of children have been found to develop milk allergy at the age of 3 years, 50% at the age of 6 years, and 28% after 9 years [30]. According to the contemporary standards of food allergy management of these children, it is necessary to use an elimination diet and monitor the state of acquiring tolerance every 6-12 months. Each negative result of the performed double-blind placebo-controlled food challenge (DBPCFC) needs the open verification method. It appears that some of the children with egg allergy and a negative DBPCFC result, in which egg is used as a lyophilisate or in a cooked form, reacts to raw egg white in the diet [31,

32]. Thus, attention has been paid to the fact that some children with food allergy demonstrate a different sensitivity to different forms of the same allergen.

It has been shown that high temperature obtained in the process of baking changes the allergenicity of some proteins, mostly through loss of conformational epitopes [33]. Moreover, not only sensitivity to temperature and the process of digestion but also interaction with other food components, the so-called “effect of food matrix”, have been found to be a significant element in acquiring tolerance to food [23]. The main allergens of milk protein sensitizing patients with cow's milk allergy are β -lactoglobulin, α -lactalbumin, bovine serum albumin, and casein. β -Lactoglobulin and bovine serum albumin are heat-labile, while α -lactalbumin and casein are heat-stable [21]. On the other hand, ovoalbumin (Gal d I), ovomucoid (Gal d III), ovotransferrin (Gal d II), and lysozyme

Table 3. Mean sIgE concentration according to type of tolerance to food allergen

	sIgE (mean \pm SD) [IU/ml]	sIgE range [IU/ml]
Children with allergy to heated allergens of		
Cow's milk protein or egg white (<i>n</i> = 8)	13.5 \pm 19.2 ^a	1.3-59
Cow's milk protein (<i>n</i> = 5)	12.8 \pm 4.5 ^d	9.2-17.9
Egg white (<i>n</i> = 3)	13.9 \pm 25.2 ^e	1.3-59
Children with tolerance to heated allergens of		
Cow's milk protein or egg white (<i>n</i> = 18)	5.2 \pm 8.5 ^b	0.7-34.2
Cow's milk protein (<i>n</i> = 9)	6.01 \pm 11.4	0.7-34.2
Egg white (<i>n</i> = 9)	4.48 \pm 0.7	3.3-5.3
Children with tolerance to heated and unheated allergens of		
Cow's milk protein or egg white (<i>n</i> = 3)	1.5 \pm 1.1 ^c	0.2-2.9
Cow's milk protein (<i>n</i> = 2)	1.55 \pm 1.9	0.2-2.9
Egg white (<i>n</i> = 1)	1.5	

^a*p* > 0.05 (children with allergy to heated cow's milk protein or egg white allergens vs. children with tolerance to heated allergens), ^b*p* = 0.049 (children with allergy to heated cow's milk or egg white allergens vs. children with tolerance to heated and unheated allergens), ^c*p* > 0.05 (children with tolerance to heated cow's milk protein or egg white allergens vs. children with tolerance to heated and unheated allergens), ^d*p* > 0.05 (children with allergy to heated cow's milk protein allergens vs children with tolerance to heated allergens), ^e*p* > 0.05 (children with allergy to heated egg white vs children with tolerance to heated allergens)

(Gal d IV) are essential constituents of egg white. Ovomucoid is relatively thermostable, while ovalbumin, ovotransferrin, and lysozyme are heat-labile. It is commonly known that cow's milk and egg allergens belonging to the so-called 8 main food allergens are thermostable. However, a reduction in the IgE bond to ovomucoid subjected to denaturation has been demonstrated [32]. That is why patients with egg allergy more quickly acquire tolerance to cooked than raw egg [34].

It has been so far suggested that "outgrowing food allergy" is possible by strict elimination of food products, and repeated exposure even to a small amount of allergen may initiate allergy development, at the same time delaying the development of tolerance [35], although these data have not been precisely documented. Recent studies indicate that a strict elimination diet is not always respected, and in spite of this fact the patients with allergy are able to outgrow it [18]. Allen suggests that certain exposure to egg allergens not only enables acquisition of tolerance but also may accelerate it [18].

Moreover, it has been shown that 75% of children with allergy to cow's milk protein or to egg white tolerate heated milk and egg products, but they do not tolerate "raw milk and egg" [21, 22]. The results of the author's own studies in which tolerance to processed milk and egg allergens was found in 69% of children with diagnosed allergy to these foods are in accordance with the above-mentioned findings. Although a potential weakness of the present study is its small sample that does not allow us to draw conclusions concerning the change in the management of the child with food allergy, the outcomes encourage us to continue the research.

Literature data indicate lower values of reactions to skin prick tests, as well as lower asIgE and higher IgG4 levels in children with tolerance to heated allergens of milk and egg which are found in their diet [21, 22]. Though the analysis of asIgE levels in the group of children examined did not reveal statistically significant differences according to the type of allergy, the highest asIgE levels were detected in children with allergy to heated allergen, lower in those with tolerance to heated allergen and the lowest in those with tolerance to heated and unheated allergen.

What is more, the severity of allergy has been found not to be associated with the degree of keeping to the recommended elimination diet [18]. The analysis of our studies has not shown any differences in severity of an allergic reaction during oral provocation tests between the heated allergen-reactive and unheated allergen-reactive children. However, it has been revealed that in unheated allergen-reactive children there were symptoms which were considered to be severe; no such symptoms were observed in children with allergy to unheated allergen, who tolerated heated allergens. The outcomes of our observations seem to be in compliance with the findings of other authors who emphasize a milder course of aller-

gy in children with tolerance to heated allergens, which may indicate a more favourable phenotype of allergy.

Shreffler has demonstrated that children with heated allergen tolerance have a higher level of allergen-specific regulatory T lymphocytes (FOXP3) and a weaker reactivity of basophils to milk allergens than those with allergy to heated allergens [36]. Changes in immune markers in allergic children during the ingestion of heated allergens are similar to the changes observed during oral immunotherapy, which suggests that this method of management may be useful in quick acquisition of tolerance.

Although the results of research on this subject are still scarce, in the guidelines for the management of egg allergy, the British Society for Allergy and Clinical Immunology has included the information that an attempt to use a well-cooked egg as a cake ingredient can be made individually mainly in the period of tolerance acquisition. Moreover, products containing eggs were divided into "well-cooked, undercooked, and raw" [37].

The results of studies on tolerance to milk products subjected to high temperature do not allow for their practical application yet because, among other things, a relatively small population has been examined until now. Furthermore, it cannot be excluded that the observed effect depends on the applied dose; 2.6 g of proteins is used in the challenge test with a heated product, while a dose of 8 g is used in the traditional challenge with unheated product. All the same, the mean dose inducing symptoms of allergy to milk protein in the traditional provocation test has been found to be 0.4 g, so it is significantly lower than the total dose in the provocation with a heated product [21].

The study by Nowak-Węgrzyn indicates the presence of 2 types of IgE-mediated allergy to cow's milk protein: type I – children with "transient" allergy; and type II – children with persistent allergy [21]. If further studies confirm these two types of allergy, the management of children with milk or egg allergy could be changed and could liberalize the strict elimination diet by introducing heated allergens into it. Undoubtedly, such a change would improve the quality of life of patients and their families.

Moreover, it should be emphasised that although high temperature decreases protein allergenicity it does not completely eliminate it. Thus the only method evaluating tolerance to heated or unheated allergen is an oral provocation test, which should always be performed under a physician's supervision in a fully protected treatment room.

Recent research suggests the possibility of modifying the current management strategy in the case of food allergy, namely, changing the elimination diet into one using heated products, which may considerably improve the quality of life of patients with allergy to cow's milk protein or egg white. However, it is still not known whether such management will decrease the frequency of allergy to milk or egg [13, 36, 38]. Furthermore, an attempt to

answer the question whether the ingestion of heated allergens may accelerate the induction of tolerance to their unheated forms requires further studies.

The latest results of investigations justify further evaluation of new methods in the treatment of food allergy. It is not known whether new therapeutic methods will prove effective and safe for all patients. Apparently, there will be patients for whom an elimination diet will be the only therapeutic option. Besides, when choosing a definite therapeutic method we should not forget about observational investigations which indicate that tolerance develops after the period of allergen avoidance, as well as about a lack of possibility of predicting which patient will severely react to a product tolerated by another patient, e.g. a product subjected to thermal processing.

Conclusions

1. About 70% of children with IgE-dependent allergy to cow's milk protein or egg white tolerate these allergens after their thermal processing, which allows us to widen the elimination diet.
2. The clinical course of allergy to milk and/or egg may be associated with the possibility of acquiring tolerance to heated allergens.
3. Evaluation of acquisition of tolerance to heated allergens in children with milk or egg allergy requires further studies.

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