

Natural history of IgE-dependent food allergy diagnosed in children during the first three years of life

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Received 09.03.2010
Accepted 16.12.2010
Advances in Medical Sciences
Vol. 56 · 2011
DOI: 10.2478/v10039-011-0008-0
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ABSTRACT

Purpose: The aim of the study was to analyze: the course of allergy diagnosed during first three years of life, frequency of food tolerance development and impact of factors which have potential meaning in that process.

Material and Methods: The study was performed in 115 children with IgE-dependent allergy, diagnosed during first three years of life, treated in 2nd Department of Pediatrics and Allergology of Polish Mothers Health Center in Lodz. All children were invited to our clinic in order to analyze course of the allergy after period of minimum 5 years since diagnosis.

Results: The results of the study revealed that food tolerance was acquired by high percentage of examined children (87.9%) among 83 children with food allergy. However among 32 children with initial inhalant allergy there were still no food sensitizations. The frequency of this process increased with age of examined children. The study revealed that such factors as lack of family history of atopy, clinical manifestation limited to one system, lack of inhalant allergy, type of allergen, good social conditions, have positive impact on tolerance development.

Conclusions: High percentage of children with food allergy is able to develop the status of food immunotolerance. Factors which predispose to development of food allergy have also negative impact on ability to acquiring tolerance to harmful food. The study indicates the need of constant and wide education about decreasing exposure to allergy predisposing factors which could increase chance of food tolerance development.

Key words: food tolerance, food allergy, children

INTRODUCTION

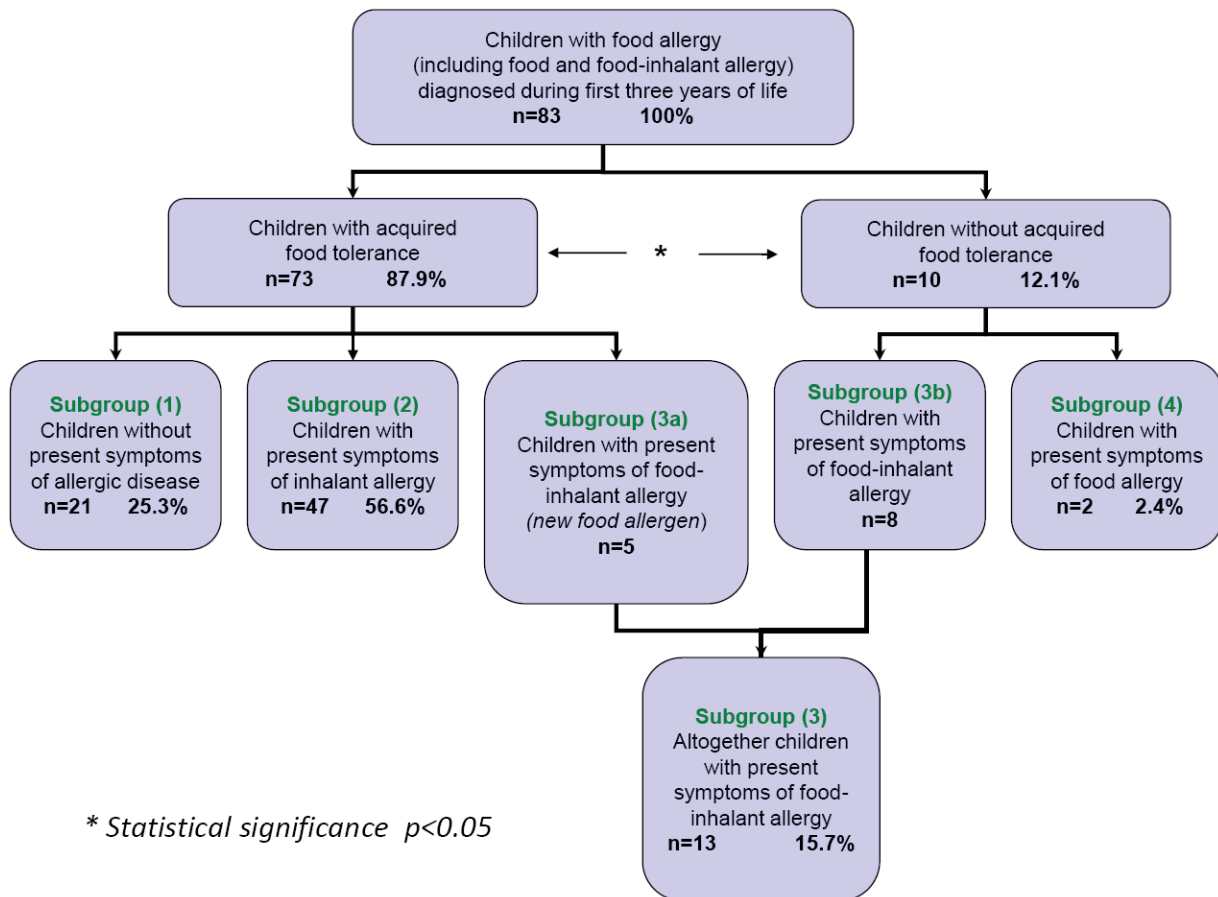
The frequency of food allergy systematically grows and it becomes a more and more important clinical issue [1]. Food allergy mostly concerns infants and small children and its frequency decreases with age [2-4].

The pathogenesis of food allergy as well as food tolerance is complex and not completely known. Immaturity of both immune system and digestive tract predispose to inappropriate immunological reaction and development of food allergy [5-7].

Immunological tolerance mechanisms are concerned as important medical issues. During the last few years there have been many medical publications dedicated to this problem. Immunological (food) tolerance aims at limiting immunological response both IgE-dependent and IgE-independent [8-11].

Important roles are played by the anergy of T lymphocytes and by mechanisms of clonal deletion. These two mechanisms are mainly used in the case of large dose of antigen administered orally. The third mechanism of immunological tolerance is active suppression, which involves regulatory T lymphocytes. Among them CD4⁺CD25⁺ lymphocytes, Tr1 lymphocytes, Th3 lymphocytes and NK lymphocytes are distinguished. Each of these cell populations is characterized by different location and method of functioning [9,11]. The most important role in food immunotolerance development seems to be played by Th3 lymphocytes, which are able to release TGF- β and IL-10 [12,13]. CD4⁺CD25⁺ lymphocytes inhibit maturation of Th2 lymphocytes, Th2 type response and increase production of IL-10 and TGF- β . Moreover, their important role in specific immunotherapy (decreasing activity of T lymphocytes) was confirmed [10,13-15].

Figure 1. Analysis of allergic disease course among examined children.



The prognosis in food allergy is rather good because of its temporary character. Majority of patients can develop tolerance to harmful food [16].

It seems that this ability can be affected by many different factors such as: type of allergen, type of allergy, proper use of elimination diet, age of allergy development as well as environmental and genetic factors.

Therefore, the aim of the study was to analyze the course of food allergy diagnosed in children during their first three years of life with special consideration of acquiring food tolerance, and the evaluation of factors which have influence on that process.

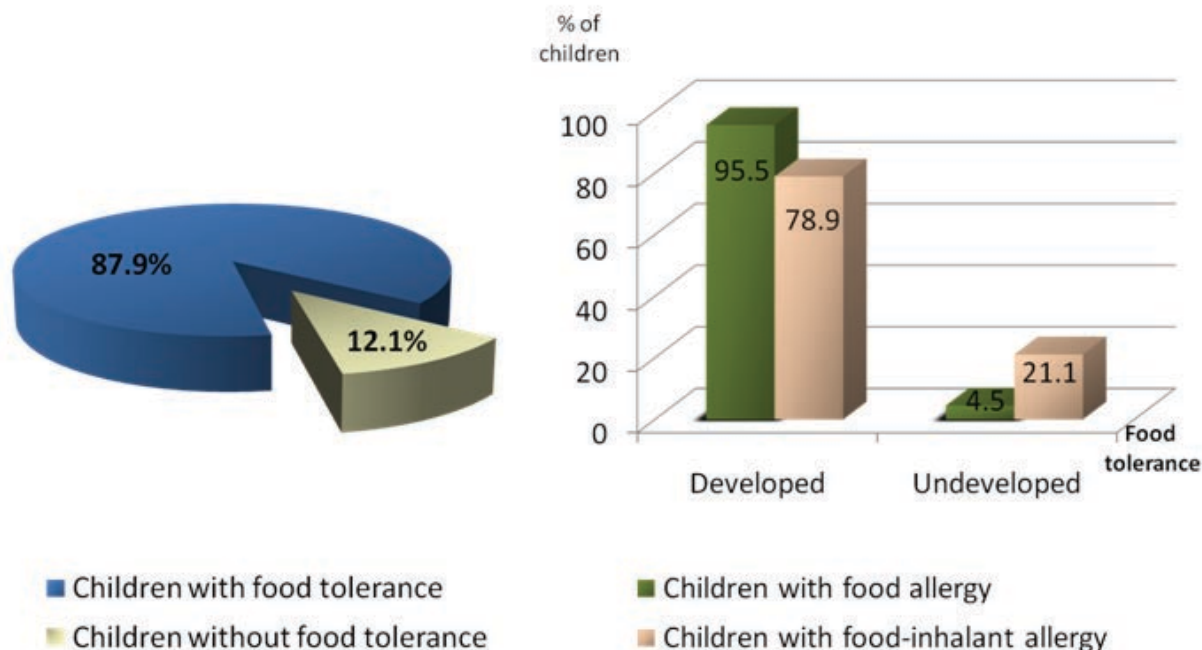
MATERIAL AND METHODS

The study was performed in 115 children with IgE-dependent allergy, diagnosed during the first three years of life, treated in 2nd Department of Pediatrics and Allergology of Research Institute of Polish Mother's Health Centre Lodz in years 1990-2001. Medical data analysis showed that the diagnosis of allergic disease was based on anamnesis, physical examination, positive elimination and provocation challenge with harmful food, and increased serum concentration of allergen-specific

IgE (at least in 2nd class). Among the examined children three groups were separated according to the type of allergy diagnosed during the first three years of life: group "P" – 45 children with food allergy, group "M" – 38 children with food and inhalant allergy, group "W" – 32 children with inhalant allergy. At present, according to the aim of the study, all the children were invited to our clinic in order to analyze the course of the allergy after a period of minimum 5 years since the diagnosis. The age of the currently examined children ranged from 5.6 to 16.9 years (average age – 11.4 years).

In the study a specially prepared questionnaire was used. The questionnaire concerned different aspects of allergy history, including clinical manifestation, intensity of symptoms, efficacy of treatment, and the occurrence of risk factors (genetic, environmental) which could also have influence on the process of acquiring food tolerance. In all the analyzed groups each child was physically examined, which showed current allergy symptoms. Besides, skin prick tests (using Alergopharma kit) were performed on them. Considering the fact that among 32 children with initial inhalant allergy no food sensitization was observed, this group of patients was not included in the analysis of food tolerance development.

The criteria of food tolerance development were: lack of clinical symptoms of allergy, good tolerance after harmful food consumption and negative results of skin prick tests. The

Figure 2. Analysis of tolerance development according to type of allergy.

age of tolerance development was defined by the moment of introducing so far harmful food into the diet and fulfilling the above mentioned criteria.

Also in each child certain chosen parameters of immune system such as: - serum concentrations of IgA, IgG with comparison of deficiency frequency between the first (during allergy diagnosis) and the second (at present) test; - serum concentrations of IgE; - lymphocytes subpopulations: T lymphocytes (CD3+), B lymphocytes (CD19+), T helpers lymphocytes (CD4+), T suppressors lymphocytes (CD8+), NK cells (CD3-/CD16+CD56+); - complement components C3, C4, total hemolytic activity (CH50); - phagocytosis of neutrophils were performed.

All the received results were statistically analyzed by Statistica 7.1. For the parameters expressed by the nominal scale, individual variants were calculated. The comparison between the groups was evaluated by chi-square test, and when the requirements were not fulfilled more accurate Fisher's test was used. In order to prove significant differences between the fractions in the tested groups, a test for two or many fractions was used.

In order to examine the correlation between the examined features, correlation series and correlation arrays were created. On their basis Spearman's rank correlation coefficient, C-Pearson contingency coefficient, T-Czuprow coefficient and V-Cramer coefficient were calculated. For the purpose of presenting the results in the publication, C-Pearson contingency coefficient (used for analysis of quantitative and qualitative features) was chosen [17,18].

In order to perform the study, the approval of Ethics Committee in Research Institute of Polish Mother's Health Centre and formal consent of parents were obtained.

RESULTS

The results of our study revealed that food tolerance was acquired by 73 children (87.9%) of 83 examined patients with allergy diagnosed during the first three years of life, including food allergy in 45 children and mixed (food and inhalant) allergy in 38 children. This process increased with the age of the examined children.

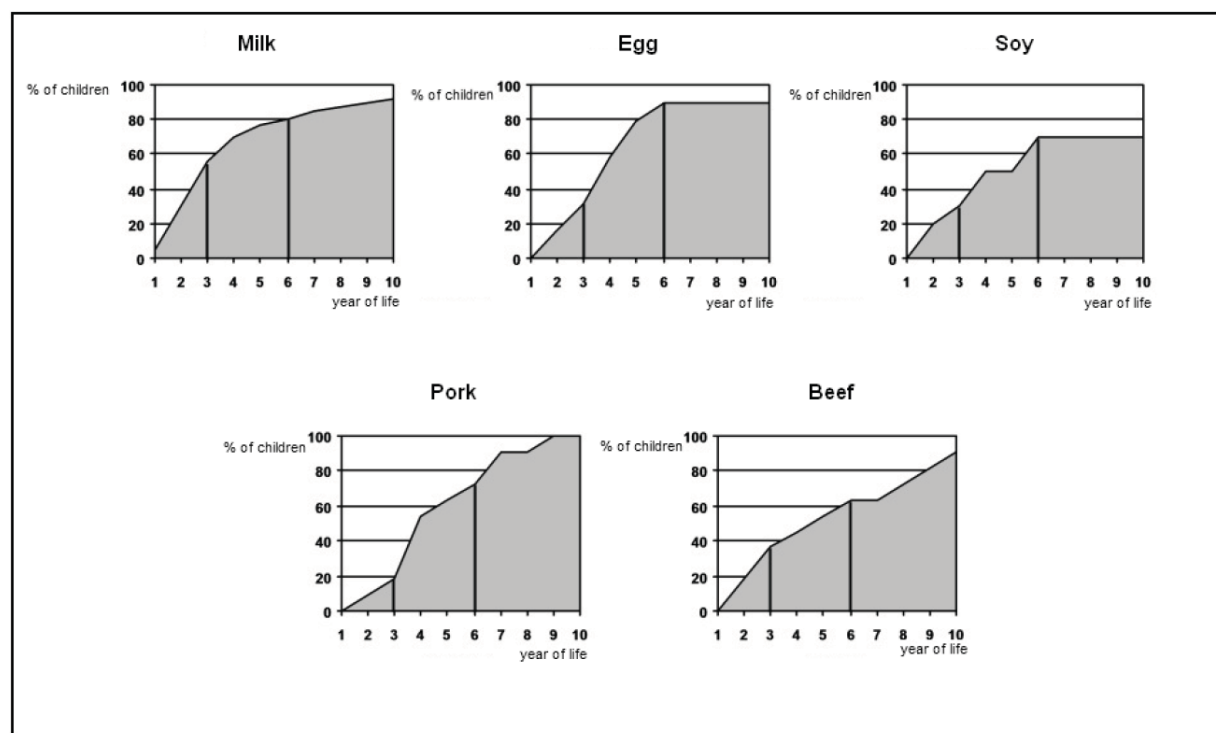
The comparison of present results and medical data of the patients allowed to analyze the natural history of the disease and to differentiate four children subgroups: 1- without current symptoms of allergic disease (n=21), 2- presenting symptoms of inhalant allergy (n=47), 3- presenting symptoms of food and inhalant allergy (n=13), 4- presenting symptoms of food allergy (n=2) (Fig. 1).

The analysis of different factors influence on the ability of food immunotolerance development showed, that the type of allergy plays an important role in that process. The children with only initial food allergy acquired food tolerance in statistically significant higher percentage (95.5%) in comparison to children with initial food and inhalant allergy (78.9%) ($p < 0.05$) (Fig. 2).

The analysis of allergen type showed that most often food allergy was caused by cow milk's proteins (47 children), white and yolk of an egg (19 children), soy (10 children), pork (11 children) and beef (11 children). All these allergens belong to the group of allergens which cause so-called "most often temporary" food allergy. There was no statistically significant difference in the quantity of food tolerance according to the type of allergen ($p > 0.05$). However, there was a difference in the speed of this process. It occurred that children with cow

Table 1. Development of food tolerance according to type of sensitizing allergen.

Tolerance development (year of life)	Type of allergen									
	Milk (n=47)		Egg (n=19)		Soy (n=10)		Pork (n=11)		Beef (n=11)	
	n	%	n	%	n	%	n	%	n	%
1	2	4.2	0	0	0	0	0	0	0	0
2	12	25.5	3	15.8	2	20.0	1	9.1	2	18.2
3	12	25.5	3	15.8	1	10.0	1	9.1	2	18.2
4	7	14.9	5	26.3	2	20.0	4	36.4	1	9.1
5	3	6.4	4	21.0	0	0	1	9.1	1	9.1
6	2	4.2	2	10.5	2	20.0	1	9.1	1	9.1
7	2	4.2	0	0	0	0	2	18.2	0	0
8	1	2.1	0	0	0	0	0	0	1	9.1
9	1	2.1	0	0	0	0	1	9.1	1	9.1
10	1	2.1	0	0	0	0	0	0	1	9.1

Figure 3. Age of tolerance development according to type of allergen.

milk allergy were able to develop food tolerance more quickly than children with other food allergies. More than a half of the sensitized patients acquired tolerance after the 3rd year of life, while in the case of other allergens comparable results were obtained after the 4th or 5th (beef) year of life (*Tab. 1; Fig. 3*).

The results of the study also showed differences in the development of tolerance after a causal treatment according to the type of allergen. Similarly as in the case of age tolerance analysis cow milk occurred to be an allergen demanding relatively shortest period of the elimination from the diet.

After one year of the eliminative diet, food tolerance was acquired by almost half of the sensitized children (46.5%) and this tendency was increasing with age (80.3% after 4 years, 91.5% after 8 years).

The analysis of the disease beginning time showed that this factor also had an impact on the tolerance development. Children suffering since the first year of life had significantly lower ability to obtain tolerance than children suffering since the third year of life ($p < 0.05$).

Table 2. Correlation strength between examined factors and acquiring of food tolerance in children with allergy.

Factors	Correlation between factors predisposing to food allergy and food tolerance development	
	C-Pearson's coefficient	statistical significance (p<0.05)
Type of allergen	0.35	<0.05
Atopy in family	0.29	<0.05
Clinical manifestation	0.27	<0.05
Type of allergy	0.25	<0.05
Age of allergy onset	0.19	>0.05
Social conditions	0.13	>0.05
Food polyallergy	0.12	>0.05
Length of breast-feeding	0.07	>0.05
asIgE class	0.07	>0.05
Frequency of respiratory tract infections	0.06	>0.05
Total IgE concentration at the beginning of allergy	0.02	>0.05
Percentage of eosinophils	0.02	>0.05

A connection between acquiring food tolerance and the exposure to the factors which have a certified influence on the development of the allergic disease, was also confirmed.

The analysis included many different factors such as family history of atopy, length of breast feeding, social conditions, exposure to indoor allergens, type of clinical manifestation concerning the amount and sort of the involved systems, food polyallergy, strength of sensitization (asIgE class according to 4-gradual atopy scale) and concentration of total IgE at the beginning of the disease.

The obtained results confirmed that the occurrence of the above-mentioned factors has not only got an impact on the allergy development but also hampers the ability of acquiring food tolerance. It seems to be logical that the lack of exposure to these factors can improve the prognosis of the disease.

Among the children who did not acquire food tolerance in comparison to those who did, there was a higher percentage of patients : with positive family history of atopy (p>0.05), with polyallergy (p<0.05) or breast-fed for a shorter time than 6 months (p<0.05); and a lower percentage of patients with good social conditions (p<0.05) or presenting symptoms concerning only one system (p<0.05).

The analysis of IgE-dependent allergy "indicators" confirmed that the percentage of children with asIgE class, higher than the second, was found more frequently among the children without the developed tolerance (10.0%) in comparison to children with the acquired tolerance (4.1%). However, the difference was not statistically significant (p>0.05). Also the evaluation of serum total IgE concentration at the beginning of the allergy showed that the children unable to develop tolerance had significantly higher levels of IgE (40.0% vs. 37.0%) (p<0.05).

The chosen parameters of the immunological system were also evaluated. The determination of serum concentrations of IgA and IgG showed that 6.9% of children had deficiency of IgA. This percentage was lower in comparison to the results

obtained during the allergy diagnosis (16.5%). This difference was statistically significant (p<0.05). There was no significant difference in the frequency of IgG deficiency (from 20.9% to 18.3%). The children who were unable to develop food tolerance had more often deficiency of IgA. These children had also significantly more frequent decreased percentage of T lymphocytes and an increased percentage of NK cells in comparison to the children with acquired tolerance (p<0.05).

The analysis of complement system parameters and neutrophils phagocytosis ability showed minor differences in the frequency of disorders (p>0.05).

Summing up, in each child the strength of correlation between the factors which predispose to allergy and the ability to develop tolerance was evaluated. The results are presented in *Tab. 2*. It was confirmed that a positive family history of atopy, type of allergen, type of allergy and clinical manifestation have an important meaning in the process of tolerance development.

DISCUSSION

Food allergy is a serious and frequent health problem, especially in very young children. It is related to physiological immaturity of lymphatic tissue, insufficiency of intestine epithelial barrier and a small activity of digestive enzymes. These disorders are the main reasons of difficulties in the tolerance development after allergen contact [4,19].

The development of food tolerance is not a common subject of scientific papers. The present knowledge about food allergy gives information about a gradual age-related "growing out" from this type of allergy. Acquiring food tolerance is a complex process which engages mechanisms of immunological system. These mechanisms are investigated by many authors [10-12,14,15,20-22].

Among the examined children food tolerance was acquired by 87.9% patients. The percentage of the children with the developed tolerance increased with age, from 2% after 1st year of life, to 78.6% after 6th year of life. These findings are similar to study results of many authors [23-31].

However, there is a small amount of studies which would try to evaluate if the factors having a certified influence on the allergy development can also modulate the process of acquiring food tolerance.

Our study showed that the children with solely food allergy acquired food tolerance earlier and in a higher percentage. It seems that a larger burden of immunological system, including the increased stimulation by additional inhalant allergens may hinder the tolerance development. However, in the available literature there are no papers concerning such dependence.

This study also revealed that the percentage of children without the acquired tolerance was higher among the patients with polyallergy (19.0%) in comparison to the children sensitized only to one food (9.7%). These findings are similar to the results of other authors who showed that sensitization to many food allergens contributes to a delay of tolerance development [32].

It seems that also the type of food allergen has a meaning in tolerance development. Many authors showed that patients sensitized to such food allergens as cow's milk, soy, the white and yolk of an egg, rye and others have relatively higher facility of acquiring tolerance [26]. In our study the allergy was mainly caused by 5 allergens: cow's milk, egg, soy, beef and pork, which are known as allergens causing so called "temporary allergies". In that case all the examined children had large and similar chances of tolerance development. However, the age of acquiring tolerance was different for particular allergens. A relatively quick tolerance development to "temporary allergens" justifies the need of frequent food challenges, which in compliance with recommendations should be performed every 6 months (before 3rd year of life) and every 12 months (after 3rd year of life) [33,34].

The study revealed that the percentage of children with the acquired tolerance was lowest among the patients ailing since 1st year of life (83.3%) and highest among the patients ailing since 3rd year of life (100%). These findings are similar to the results of other authors, who also showed that the diagnosis of food allergy in the early period of life is inversely proportional to the tolerance development. According to these authors, it seems that the immaturity of immunological system and morphological-functional immaturity of the digestive tract do not only favor the allergy development, but can also cause a heavier course of the disease [24,35] which, in turn, may hinder acquiring food tolerance. A genetic factors influence on the allergy development is widely presented in medical literature [36-38]. The results of the study showed that the percentage of children with positive family history of atopy was significantly higher (70%) among the patients without the acquired tolerance in comparison to the children with the acquired tolerance (30%). Our results are similar to

the observations made by Savage [29] and Cantani [24] which showed that the genetic factors play an important role in the hindrance of tolerance development.

Next, the relationship between the environmental factors and the course of the disease as well as growing out of it was examined. It was found out that the percentage of the children with good social conditions was higher among the patients, who acquired food tolerance (35.6%). Inversely, more children with bad social conditions were among the patients without developed food tolerance. These findings, by showing opposite relations, correspond to the conclusions of many authors who showed an important role of bad environmental conditions in the development and course of allergic disease [36,38,39].

Many scientific papers described different clinical manifestations of allergy, depending on the type of allergy and age of children [40-43].

In our study the relation between the development of food tolerance and number of engaged systems was shown. All the children, who did not acquire food tolerance at the beginning of the disease presented symptoms from at least two systems, while among the children with the developed tolerance this percentage was significantly lower (67.1%). This observation suggests that the type of clinical manifestation has a certain value in the forecasting of tolerance development [44].

Some authors indicate that asIgE concentration can have predictive value for the course of disease [24,28,32,45]. Our findings were similar and showed that among the children with the acquired food tolerance the percentage of the patients with asIgE class above 2nd was lower (4.1%) in comparison to the children without the developed tolerance (10.0%).

The concentration of IgE can be regarded as a laboratory marker in the children with food hypersensitivity, however, normal levels of IgE do not exclude allergic process. Our study showed, that a higher percentage of children with increased levels of IgE was observed among the patients who did not acquire food tolerance (40.0%). The results of other authors' studies are miscellaneous. Imai *et al.* [32] showed a lack of influence while Cantani *et al.* [24] confirmed the influence of IgE on the tolerance development.

An impact of immunoglobulin deficiency on the tolerance development was also considered. The results revealed that significantly more children with IgA deficiency were among the patients who did not acquire tolerance during the period of observation.

The estimation of the analyzed factors influence on the development of food tolerance showed that a negative family history of atopy had the most important meaning. A significant role was also played by the type of allergen, type of allergy and clinical manifestation of the disease. These findings are similar to other authors' results. Cantani *et al.* [24] emphasize the important role of the family history, early onset of the disease and a high concentration of total IgE and asIgE. Imai *et al.* [32] and Czaja-Bulsa *et al.* [25] showed the importance of polyallergy.

CONCLUSIONS

A high percentage (87.9%) of children with food allergy is able to develop the status of food immunotolerance. Maturation of immunologic system with age plays important role in the process of acquiring food tolerance. Factors which predispose to development of food allergy have also negative impact on ability to acquiring tolerance to harmful food. The study indicates the need of constant and wide education about decreasing exposure to allergy predisposing factors which could increase chance of food tolerance development.

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