IgE- AND NON-IgE MEDIATED FOOD ALLERGY IN CHILDREN

R. Ciorap, Ecaterina Anisie¹, Celina Stafie², Dana Elena Mindru³, Anca Hâisan⁴, Evelina Moraru⁵, Monica Ungureanu²*

University of Medicine and Pharmacy “Grigore T. Popa”- Iaşi
Faculty of Bioengineering
1. Department of Biomedical Science
Faculty of Medicine
2. Department of Preventive Medicine and Interdisciplinarity
3. Department of Mother and Child Medicine
4. Department of Medical Specialties (II)
“Sf. Spiridon” Emergency Clinical Hospital, Iasi
5. Immunology Laboratory

*Corresponding author. E-mail: ungureanu_monica73@yahoo.com

IgE- AND NON-IgE MEDIATED FOOD ALLERGY IN CHILDREN (Abstract). Aim: To evaluate a group of children diagnosed with food allergies mediated by IgE or non-IgE mechanisms. Material and Methods: This retrospective study was conducted on 132 patients diagnosed with food-associated hives admitted over a 2-year period to the Pediatric Clinic II of the Iasi “St. Maria” Children’s Hospital. Results: Serum levels of specific IgE were positive in 85 (64.39%) cases for one or more food allergens, while positive values of IgG4 were recorded in 21 (15.9%) cases. The most commonly involved allergens were cow milk, egg white, peanuts, wheat flour and fish, in agreement with data in the literature. Percentage frequency of risk factors for allergic sensitization was: artificial or mixed feeding (68.18%), family history of atopy (53.78%), food diversification before 6 months of age (52.27%), natural feeding for less than 3 months (37.87%), and prolonged antibiotic therapy (23.48%). Polysensitization to food and airborne allergens correlated with respiratory allergic manifestations (asthma and allergic rhinitis), occurring predominantly in the age group over 4 years, while atopic dermatitis was associated with food allergy in children up to 4 years of age. Conclusions: This study shows that IgE-mediated food allergies are more common, with a higher frequency in children below 4 years due to the interaction of genetic and environmental factors and immaturity of the immune system in the first years of life. Keywords: FOOD ALLERGENS, IMMUNE MECHANISMS, IgG4 ANTIBODIES.

The prevalence of allergic diseases has increased in recent decades due to changes in eating behavior, involvement of environmental agents and infectious factors.

The most common cause of sensitization is food-related, the cutaneous, digestive and respiratory allergic manifestations developing concurrently or alternately.

Food allergy is defined as "a phenomenon in which adverse reactions are caused through antigen-specific immunological mechanisms after exposure to given food" (1).

The etiopathogenic factors involved in food allergy and therapeutic possibilities are important research goals.
**MATERIAL AND METHODS**

This retrospective study was conducted on 132 patients diagnosed with food-associated hives admitted over a 2-year period to the Pediatric Clinic II of the Iasi "St. Maria" Children's Hospital.

Total IgE was measured by ELISA, and the determination of serum specific IgE specific to 20 of the most common food and airborne allergens by CLA System Quanti Scan (Innogenetics, Heiden, Germany).

An enzyme immunoassay for the quantitative determination of IgG4 antibodies against 20 food allergens was performed using Fin Test Kit TM IgG4 Screen ELISA 20. The tested allergens were: egg white, cow milk, fish, wheat flour, rye flour, barley flour, orange, banana, kiwi, strawberry, celery, soy, carrot, tomato, hazelnuts, peanuts, curry, pepper, sesame, and pork. Cutaneous testing was done with skin prick test for 7 food allergens (milk, egg, wheat, hazelnuts, nuts, fish, soy).

Statistical analysis was performed using statistical software SPSS10.0, and data were analyzed using descriptive and inferential statistics (Student t test).

**RESULTS**

Age group distribution showed that predominantly affected were the children aged under 4 years, 93 (70.45%) cases. The mean age at admission was 30 months.

Percent frequency of risk factors for allergic sensitization was as follows: artificial or mixed feeding (68.18%), family history of atopy (53.78%), food diversification before 6 months of age (52.27%), natural feeding for less than 3 months (37.87%), and prolonged antibiotic therapy (23.48%) (fig.1).

![Percent frequency of risk factors for allergic sensitization](image)

**Fig. 1. Hierarchy of risk factors for allergic sensitization**

All patients (132) presented hives-like skin manifestations, while associated digestive and respiratory manifestations were present in 18 (13.63%) and 16 (11.36%) cases, respectively.

The associated allergic manifestations were: atopic dermatitis in 22 (16.66%) cases, asthma 11 (8.33%) cases, angioedema 36 (27.27%) and allergic rhinitis in 5 (3.78%) cases.

In 85 (64.39%) cases specific IgE were positive for one or more food allergens. The allergens most commonly involved were: cow milk 28 cases (21.21%, p =
R. Ciorap et al.

0.000), egg white 19 cases (14.39%, p = 0.000), peanuts 10 cases (7.57%, p = 0.000), fish 8 cases (6%, p = 0.000), soy 6 cases (4.54%, p = 0.000), nuts 6 cases (4.54%, p = 0.000), wheat flour 5 cases (3.78%, p = 0.003), strawberries 2 cases (1.51%, p = 0.011) and rye flour 1 case (0.75%, p = 0.150).

All allergens were statistically significant except for rye flour (p = 0.150) (fig. 2).

Fig. 2. The most common specific IgE allergens

In patients with low specific IgE levels but in which clinical manifestations and history were suggestive of allergy (47 cases - 35.60%), IgG4 antibodies against 20 food allergens were determined. Of these, 21 (15.9%) cases showed positive IgG4 levels against the following allergens: wheat flour (5 cases, p = 0.049), cow milk (3 cases, p = 0.072), egg white (2 cases, p = 0.061), peanuts (3 cases, p = 0.064), rye flour (2 cases, p = 0.040), strawberries (2 cases, p = 0.108), nuts (2 cases, p = 0.027), fish (1 case, p = 0.006) and soy (1 case, p = 0.087) (fig. 3). One patient presented mixed allergy to peanuts and nuts.

Of these allergens only wheat flour only (p = 0.049), rye flour (p = 0.040) and fish (p = 0.006) were statistically significant.

Fig. 3. The most common specific IgG4 allergens
IgE- and non-IgE mediated food allergy in children

In patients with positive IgG4 levels to different food allergens, 89% presented associated digestive and cutaneous symptoms, suggesting that the level of specific IgG4 antibodies is high in patients with gastrointestinal allergy, but has no predictive value.

Polysensitization to food and airborne allergens correlated with respiratory allergic manifestations (asthma and allergic rhinitis), occurring predominantly in the age group over 4 years, while atopic dermatitis was associated with food allergy in children under 4 years.

The reference values for specific IgG4 antibodies are listed in table I.

**TABLE I**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>REFERENCE VALUE</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.35 U/mL</td>
<td>negative - no IgG4 antibodies detected</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.7 U/mL</td>
<td>borderline - low level of IgG4 antibodies</td>
</tr>
<tr>
<td>2</td>
<td>0.7-3.5 U/mL</td>
<td>positive - moderate level of IgG4 antibodies</td>
</tr>
<tr>
<td>3</td>
<td>3.5-17.5 U/mL</td>
<td>distinctly positive - high level of antibodies</td>
</tr>
<tr>
<td>4</td>
<td>&gt;17.5 U/mL</td>
<td>Highly positive - very high levels of IgG4 antibodies</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Food allergy is defined as an immune response to food proteins affecting approximately 8% of children and 2% of adults (2), but it’s the prevalence, as well as that of all allergic diseases is increasing.

In food allergy the mechanisms involved may be IgE or non-IgE mediated immune reactions. The immune mechanisms involved in non-IgE mediated reactions may be based on the participation of subtype 4 IgG antibodies. These types of IgG4 antibody mediated reactions are characterized by less severe and less specific symptoms, and have a late onset after the intake of the incriminated food (up to 72 hours).

There are several arguments supporting the involvement of IgG4 antibodies in non-IgE mediated food allergies: allergic reactions may occur independently of IgE specific antigen; subsequent decline of IgG antibody level when the incriminated food is removed from diet; specific IgG antibodies were identified in celiac disease, atopic eczema and in diseases associated with increased intestinal permeability (chronic inflammatory bowel disease) (3).

Besides hives and anaphylaxis triggered by IgE-mediated immune mechanisms, there are several cell-mediated diseases, such as food protein-induced eosinophilic esophagitis or enterocolitis. Non-IgE mediated food allergies that manifest with food protein-induced enterocolitis syndrome or eosinophilic esophagitis are rare and have a favorable course on elimination diet (4).

Immune-mediated food allergies have to be distinguished from food intolerances caused by non-immune mechanism which are non-specific and their symptoms and those of irritable bowel syndrome often overlap (5). Allergic diseases by food sensitization are more common in the early years of life, their frequency decreasing with age, with the acquisition of tolerance.
to food. Allergic manifestations with onset in the early years of life are the result of the interaction between genetic factors, environmental factors (artificial feeding, incorrect diversification, prolonged antibiotic therapy) and immaturity of the immune system in early childhood (6).

In our study group the diagnosis of food allergy was based on the criteria in international guidelines, suggestive clinical manifestations, thorough history, and positive levels of serum specific IgE and IgG4 against food allergens, positive skin tests, elimination diet, and oral loading test. The latter must be done under close medical supervision as it can cause such severe adverse reactions as anaphylaxis.

The analysis of specific IgE and IgG4 shows that 64.39% of the cases were IgE-mediated allergies and 15.9% IgG4-mediated allergies. The allergens most frequently involved were cow milk (p = 0.000), egg white (p = 0.000), peanuts (p = 0.000), wheat flour (p = 0.003) and fish (p = 0.000), in agreement with the data in literature (4, 7, 8). Correlation of skin test with specific IgE level showed a concordance between results. Skin tests have a sensitivity of 95% and a specificity of 50% (9). A negative skin test result has a high predictive value in children older than 1 year, while in children less than 1 year its negative predictive value is lower due to the particularities of cutaneous mast cells (small number and low reactivity). A positive skin test has a positive predictive value of only 50%. If history is not strongly suggestive of an allergy, the diagnosis should be confirmed by a challenge test (10).

With regard to egg allergy, recent studies estimate that it affects approximately 0.5-2.5% of children (11, 12), but there are studies reporting a higher percentage; thus, an Australian study suggests that 8.9% of children have allergic reactions to egg (13). In our study egg allergy is the second most common food allergy. Egg allergy is associated with a high risk of allergy to peanuts or other food allergens, atopic dermatitis, occurrence of respiratory allergy and asthma (14, 15, 16). The rate of resolution of egg allergy is slow; most studies show that tolerance to egg develops at age 3 (17), but there are studies suggesting that about half of children develop tolerance at age 12 (18). The latter study demonstrated persistent egg allergy in 42% of children in their teens, suggesting that the number of adults with egg allergy can increase with time, although current estimate of egg allergy among adults is 0.2% (19).

Factors predictive of the resolution of egg allergy are: initial reaction characteristics (isolated hives/angioedema versus other events), specific IgE level, intensity of skin prick test reaction, severity of atopic dermatitis, IgG4 level, response of interleukin 4 (IL-4). Of these, the first two are the most important predictors for resolution (11).

CONCLUSIONS

This study shows that IgE-mediated food allergies are more common, the highest percentage being recorded in children less than 4 years of age due to the interaction of genetic and environmental factors and immaturity of immune system in the early years.

This work received financial support from the European Social Fund Operational Programme Human Resources Development 2007-2013, contract no. POSDRU/159/1.5/S/133377.
REFERENCES