Difficulties in Differential Diagnosis of Skin Allergies in Children

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Abstract

The article presents the data from recent literature and personal, practical experience of differential diagnosis of skin allergies in children. The difficulties detected at various stages of the disease diagnosis with the need for differentiation of allergic diseases (food allergy, atopic dermatitis, urticaria, insect allergy) and non-allergic genesis are: viral infections with skin lesions (herpes, chicken pox, measles, infectious erythema, hand foot mouth disease), bacterial infections of the skin (strep- and staphylocemia), and a group of other diseases (ichthyosis, scabies, psoriasis). It also should be mentioned that special emphasis on diagnosis belongs to food hypersensitivity, which combines immunological and non-immunologic reactions.

An example of the observation of 60 children with skin allergies shows the approach to the investigation of the diagnosis and the difficulties that arose during this. All children were ill for more than 3 months, and at the time of inclusion in the research, there were no identified causes of the disease. The diagnostic algorithm included three stages: clinical (detailed collection of complaints and anamnestic data), laboratory (general blood test, biochemical and coprological examination, determination of total IgE and specific IgE to gluten and different milk fractions, serological biomarkers of celiac disease) and instrumental. For 14 days before blood collection patients underwent an elimination test.
The results of the study showed that in the study group of children aged 1-5 years the main diagnosis was atopic dermatitis (36.84%), food allergy (24.56%), lactase deficiency (7.02%), helminthiasis (7.02%), streptodermia (5.25%), celiac disease (3.51%).

The need for an individual approach to the laboratory-instrumental algorithm of skin allergies was described, and the results of our personal approach to the diagnosis were shown.

Keywords: children, skin allergy, diagnosis

Introduction

The problem of allergic diseases remains a priority for many years in the pediatric practice in the world [5]. According to WHO, from the year 2010, the prevalence of allergy has become an epidemic and is characterized by the deterioration of its clinical structure [6]. In Ukraine, the establishment of the diagnosis of allergic diseases, including skin allergies, is usually late. It should be noted that this situation occurs even in families where even parents suffer from allergic diseases [1].

Skin allergies - a term that combines various clinical signs of allergic skin lesions that develop as a result of the congenital hypersensitivity or sensitization of the body to different allergens (food, household allergens, herbs, trees, fungi, medicines, etc.) [5].

The analysis of the leading causes of this "allergic" epidemic has shown that the main factors are the effects of megacities, deterioration of the environmental conditions, inappropriate nutrition, stresses, uncontrolled use of medicines, passive and active tobacco smoking [3, 6]. In practice, the differential diagnosis of skin allergies is quite wide. The distinction is made with other allergic diseases (food allergy, atopic dermatitis, urticaria, insect allergy). Among the non-allergic diseases are viral infections with skin lesions (eczema herpeticum, chicken pox, measles, infectious erythema, hand foot mouth disease), bacterial skin infections (strept- and staphylococdermia), and others (ichthyosis, scabies, psoriasis) [5, 7]. On the verge of allergic and non-allergic diseases in the context of the differential diagnosis of skin allergies, food hypersensitivity, which combines immunological and non-immunological reactions should be actively considered.

Types of food hypersensitivity:
I. Immunological reactions (allergic hypersensitivity):
   - IgE-dependent (anaphylaxis, acute urticaria, oral allergy syndrome);
   - IgE-independent, cellular reactions (celiac disease);
   - IgE-dependent and IgE-independent, mixed types (eosinophilic gastritis and enterocolitis, atopic dermatitis);
II. Non-immunological reactions - non-allergic hypersensitivity (food intolerance):
   - metabolic (intolerance to lactose);
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- pharmacological (tyramine - cheeses, pickled herbs, caffeine, theobromine - chocolate, tea, coca cola; histamine - fish, fermented cabbage; tryptamine - tomatoes, plums; serotonin - bananas, tomatoes);
- toxic (toxins of fish of the family of mackerel);
- other idiopathic unclassified allergens (sulfites) [5].

The situation mentioned above has determined the relevance and purpose of our study.

Aim of the study was to optimize the algorithm for the diagnosis of skin allergies in children.

Materials and methods. We surveyed 60 children with skin allergies who have been ill for more than three months and have no identified causes of the disease.

Criteria for inclusion in the study were:
- the age of the child 1 - 5 years;
- rash over the body with the rash duration for more than 3 months; the possibility of conducting an elimination test (maintaining the hypoallergenic and gluten-free diet for 2 weeks); parent's consent for the child's participation in the study.

Exclusion criteria: severe concomitant diseases, refusal to conduct an elimination test or blood collection.

The diagnostic algorithm included three stages: clinical, laboratory and instrumental.

At the first (clinical) stage, a careful collection of anamnesis was performed. The patient's complaints with the emphasis on the problems with changes in the skin and the gastrointestinal tract, as well as data on family history were analyzed.

The second (diagnostic) stage was based on a comprehensive laboratory examination.

A general blood test and a biochemical examination (total protein, ALT, AST, glucose, total bilirubin, creatinine, urea) were conducted.

Immuno-enzyme analysis with the definition of the total IgE and specific IgE to gluten and various milk fractions (milk, α-lactalbumin, β-lactoglobulin, casein, bovine serum albumin), as well as specific serological biomarkers of celiac disease: IgA antibodies to gliadin; antibodies to gliadin IgG; antibodies to tissue IgG transglutaminase; antibodies to tissue IgG transglutaminase (Biocheck GmbH, Germany).

Comprehensive coprological examination.

The third (instrumental) stage included the skin allergy test - prick-test-in the period when the disease was controlled. In people with positive results of the serological examination (high titers of antibodies in the blood serum), endoscopy with subsequent histological analysis of gastrointestinal mucosal biopsies were conducted.

All patients were prescribed to undergo an elimination test, which consisted of the maintenance of a hypoallergenic and gluten-free diet for 14 days. It was recommended that the child's diet included vegetables (carrots, potatoes, broccoli, zucchini, cauliflower, onions, legumes), fruits, whole grains (rice, buckwheat, corn), rabbit meat, salt, sugar, oils without preservatives, dairy products
(without taste additives), non-carbonated mineral water, black non-aromatised tea [2, 4].

The study group consisted of 60 children. The patients were observed in the conditions of the Lviv City Children's Allergology Center on the basis of the Communal City Children's Clinical Hospital for 3 months.

The monitoring of the course of the disease was carried out at the start of the study and at 1, 2, 3 months on the basis of clinical symptoms, assessment of the nature and prevalence of rash, the intensity of the itching and the quality of life of patients.

**Results**

In the course of the study, 12 (20%) patients needed additional laboratory tests. In 9 (15%) patients, it was not possible to conduct skin test due to the persistent exacerbation; therefore, the levels of specific IgE to the domestic, epidermal and food allergens in blood serum were identified in these children. Some children underwent a bacteriological skin scraping (n = 7, 11.67%), skin scraping for microscopic analysis (n = 5, 8.33%), testing for the levels of antibodies to helminthes: toxocariasis, ascarids, lamblia (n = 4, 6, 67%), level of the IgA antibodies to endomysium (n = 4, 6.67%), IgM and IgG antibodies to herpes simplex 1/2 (n = 2, 3.33%), determination of IgM and IgG antibodies to Borrelia burgdorferi ( n = 1; 1.67%), the levels of diamine oxidase (n = 1, 1.67%).

At the time of the completion of the study three children were excluded from the research: 1 - refused to continue, 1 - changed the place of residence, 1 - fell ill with measles.

The diagnosis of "skin allergy" (n = 57) was found in patients as follows:
- 21 (36.84) - atopic dermatitis;
- 7 (12.28%) - allergy to cow's milk protein;
- 5 (8.77%) - allergy to other groups of allergens (eggs, soy beans, fish, peanuts, domestic dust mites, fur animals);
- 4 (7.02%) - lactase deficiency;
- 4 (7.02%) - helminthiasis;
- 3 (5.25%) - streptodermia;
- 2 (3.51%) - allergy to gluten;
- 2 (3.51%) - celiac disease;
- 2 (3.51%) - scabies;
- 1 (1.75%) - hypersensitivity to food additives (E102);
- 1 (1.75%) - erythema nodosum;
- 1 (1.75%) - chronic urticaria;
- 1 (1.75%) - eczema herpeticum;
- 1 (1.75%) - Lyme disease;
- 2 (3.51%) - the cause could not be identified (further search is being carried out).
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Food allergy in children of the study group combines allergy to cow's milk protein, gluten, eggs, soy, fish, peanuts.

Sensitization of various levels to cow's milk protein was detected in 28 (46.67%) children. All children of this group underwent oral provocation tests. True allergy to cow's milk protein was confirmed in 7 (12.28%) patients and was mainly related to casein (Bos d8), which is the thermostable and the heaviest protein in milk (Table 1) [5].

Table 1.
Characteristics of the main cow’s milk proteins

<table>
<thead>
<tr>
<th>Milk protein</th>
<th>Concentration in milk (g/l)</th>
<th>Molecular weight (kDa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% Serum (around 5 g/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% β-lactoglobulin (Bos d5)</td>
<td>3 – 4</td>
<td>18.3</td>
</tr>
<tr>
<td>5% α-lactalbumin (Bos d4)</td>
<td>1 – 1.5</td>
<td>14.2</td>
</tr>
<tr>
<td>3% immunoglobulin Bos d7</td>
<td>0.6 - 1.0</td>
<td>150</td>
</tr>
<tr>
<td>1% Bovine serum albumin (Bos d6)</td>
<td>0.1 – 0.4</td>
<td>66.3</td>
</tr>
<tr>
<td>Traces of lactoferrin</td>
<td>0.09</td>
<td>80</td>
</tr>
<tr>
<td>80% Total casein (around 30 g/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32% αS1-casein</td>
<td>12 – 15</td>
<td>23.6</td>
</tr>
<tr>
<td>10% αS2-casein</td>
<td>3 – 4</td>
<td>25.2</td>
</tr>
<tr>
<td>28% β-casein</td>
<td>9 – 11</td>
<td>24.0</td>
</tr>
<tr>
<td>10% κ-casein</td>
<td>3 – 4</td>
<td>19.0</td>
</tr>
</tbody>
</table>

It should be remembered that in children with persistent skin allergy the possibility of identifying serum markers of celiac disease need to be taken into consideration [4, 7]. Due to the conducted examinations, it was possible to detect two seropositive children in both celiac disease biomarkers. Patients were referred to a gastroenterologist, and a further endoscopic investigation with a biopsy (two confirmed celiac disease diagnosis) was conducted. In general, the titer of IgA / IgG gliadin antibodies was questionable in 7 (11.67%) and positive in 1 (1.67%) patient in the study group. However, in these children, IgA / IgG tissue transglutaminase and IgA endomysial antibodies were negative. This situation
indicates the gluten intolerance without celiac disease. Gluten-allergy was detected in 2 (3.51%) patients, which was confirmed by an oral provocation test. Table 2 shows the differential diagnosis of various conditions associated with gluten intolerance [1, 8].

**Table 2.**
Differential diagnosis of various conditions associated with gluten intolerance

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Gluten allergy</th>
<th>Gluten intolerance without celiac disease</th>
<th>Celiac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>The cause of the disease</td>
<td>Food intolerance, which may change with age</td>
<td>Genetic - deformation of intestinal villi occurs, resulting in poor absorption of the food, but the mucus membrane is not damaged.</td>
<td>Genetic - the absence of an enzyme responsible for the cleavage of gluten. Foods that contain gluten damage the intestinal villi (lead to atrophy).</td>
</tr>
<tr>
<td>Skin symptoms</td>
<td>Rash, skin itching</td>
<td>Possible rashes</td>
<td>Possible rashes</td>
</tr>
<tr>
<td>Digestive tract symptoms</td>
<td>Possible dyspepsia - pain, discomfort in the epigastrium, nausea</td>
<td>Diarrhea, weight loss, abdominal pain, flatulence</td>
<td>Chronic diarrhea, abdominal pain, flatulence, feces with a sharp odor</td>
</tr>
<tr>
<td>The need to maintain a gluten-free diet</td>
<td>Temporary</td>
<td>Life-long</td>
<td>Life-long</td>
</tr>
</tbody>
</table>
Table 2. (Continued):
Differential diagnosis of various conditions associated with gluten intolerance

<table>
<thead>
<tr>
<th>Serology</th>
<th>Positive</th>
<th>Negative</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE antibodies to wheat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA/IgG antibodies to gliadin</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>IgA antibodies to tissue transglutaminase</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>IgA antibodies to endomysium</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Genotype HLA DQ2/DQ8</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

After identifying the cause of the disease, patients were prescribed an appropriate treatment plan. In general, 38 (63.34%) received antihistamines, 7 (11.67%) - antibacterial therapy, 6 (10%) - antiparasitic therapy, 1 (1.67%) - antiviral drugs. Local therapy was used in 32 (53.33%) patients - antibacterial, antifungal, antiviral and immunologic agents and emollients.

39 (65%) patients are maintaining a diet, while the nature of the diet depends on the cause - hypoallergenic, dairy-free, gluten-free, etc.

Results at the end of the study: 32 (53.33%) patients continued the prescribed treatment with positive dynamics, 23 (38.34%) - recovered, 3 (5%) were excluded and 2 (3.33%) - conditions without significant dynamic changes, the diagnostic search continues.

We summed up the main criteria of the differential diagnostic algorithm for allergic and infectious skin lesions in Table 3 [5, 6].
Table 3.
Differential diagnostic algorithm for allergic and infectious skin lesions

<table>
<thead>
<tr>
<th>Clinical and paraclinical signs of the disease</th>
<th>Allergic etiology</th>
<th>Infectious etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of allergic disease</td>
<td>Very often</td>
<td>Seldom</td>
</tr>
<tr>
<td>Non-pulmonary allergic manifestations</td>
<td>Often</td>
<td>Seldom</td>
</tr>
<tr>
<td>Sustained recurrent course of the disease</td>
<td>Typical</td>
<td>Not typical</td>
</tr>
<tr>
<td>Homogeneity of clinical manifestations</td>
<td>Typical</td>
<td>Various clinical manifestations</td>
</tr>
<tr>
<td>Reduction and disappearance of clinical manifestations with the exclusion of a suspected allergen</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fever</td>
<td>Usually absent</td>
<td>Usually present</td>
</tr>
<tr>
<td>Child's behaviour</td>
<td>Excitement, hyperactivity, talkativeness</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Appetite</td>
<td>The same</td>
<td>Bad</td>
</tr>
<tr>
<td>Blood tests</td>
<td>Eosinophilia in the subacute period or during remission</td>
<td>Signs of a viral and bacterial infection</td>
</tr>
</tbody>
</table>
Table 3. (Continued):
Differential diagnostic algorithm for allergic and infectious skin lesions

<table>
<thead>
<tr>
<th>Effectiveness of the prescribed antibacterial therapy</th>
<th>Absent</th>
<th>May have a good effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness of the prescribed antihistamines</td>
<td>Good</td>
<td>Absent or satisfactory</td>
</tr>
<tr>
<td>Positive tests for allergic diagnosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ig E blood serum levels</td>
<td>Increased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Conclusions

The diagnosis of "skin allergy" requires a further explanation and investigation. The diagnostic algorithm should include:
1. Clinical features.
2. Conduction of an elimination test (determination of the cause-effect relationship between taking a specific food and clinical symptoms, which is essential for the preliminary identification of harmful food products) and, if necessary, an oral provocation test.
3. Laboratory data (eosinophilia - in the subacute period of the allergic process or during remission, increase in the level of total and allergen-specific IgE in the blood serum), skin allergy tests in the period of remission (negative results can exclude IgE-dependent food allergy).
4. Additional specific examinations, depending on the nature of the complaints. In the case of ineffective treatment or the inability of verifying the diagnosis in the context of skin allergies, it is necessary to remember about the determination of serological biomarkers of celiac disease and the exclusion of the infectious factor (viral, bacterial, parasitic, etc.).

Acknowledgments. We are grateful to the children and their parents for participating in the study.

Conflict of interest. The authors have no conflict of interests to disclose.

References

[1] E. Gubskaya, Sero-negative celiac disease or intolerance to gluten without celiac disease? Differential diagnosis of celiac disease and gluten intolerance
without celiac disease based on the results of personal observations, Scientific Bulletin of the National Medical University named after A.O. Bogomolets – 2013, no. 4, 54-58.


[6] The European Academy of Allergy and Clinical Immunology is in the process of developing the EAACI Guidelines for Allergen Immunotherapy for IgE-mediated food allergy, *Clinical and Translational Allergy*, 6 (2016), 24.


Received: February 1, 2019; Published: April 2, 2019