BRITISH MEDICAL JOURNAL

British Medical Journal

Volume 2, No.2, April 2022

Internet address: http://ejournals.id/index.php/bmj
E-mail: info@ejournals.id
Published by British Medical Journal
Issued Bimonthly
3 knoll drive. London. N14 5LU United Kingdom
+44 7542 987055

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CLINICAL-IMMUNOLOGICAL AND MEDICO-SOCIAL ASPECTS OF ALLERGIC DISEASES IN CHILDREN, DEVELOPMENT OF CRITERIA FOR EARLY DIAGNOSIS AND PROGNOSIS OF THE COURSE OF THE DISEASE(LITERATURE REVIEW)

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Abstract: The growing number of patients with allergic diseases, which are based on food allergies, has become one of the leading problems of the XXI century. The expansion of the spectrum of food allergens responsible for the development of food allergies raises the question of increasing knowledge in this area for practitioners. The article presents data on causally significant food allergens and food additives that cause the development of food allergies, as well as information on the main food proteins and their components involved in the formation of cross-reactivity. Modern methods of molecular diagnostics and an algorithm for diagnosing food allergies and food intolerances are presented.

Keywords: food allergy, food allergens, diagnostics.

Introduction. The relevance of the problem of food allergy (PA) at the present stage is confirmed by national documents (programs) adopted in many countries of the world, the main purpose of which is to educate practitioners about the latest achievements in the field of its diagnosis, therapy and prevention [1-5]. These documents emphasize the importance of developing more accurate diagnostic methods (molecular diagnostics) and the search for biomarkers PA to prevent the development of severe clinical manifestations of the disease and improve the quality of life of patients [1-5]. Such a high significance of this problem is due to the fact that in recent years the incidence of allergic diseases, including PA, has significantly increased worldwide, and among the causes of life -threatening conditions (anaphylaxis), food products/allergens have become one of the leading places [6-8]. PA often accompanies diseases such as bronchial asthma, atopic dermatitis, angioedema, and urti caria. Patients with these diseases are more likely to develop acute emergencies that require intensive and/or resuscitation care, which increases the cost of the healthcare system. There is a growing number of patients with eosinophilic gastrointestinal manifestations of PA, which cause the greatest difficulties in diagnosing and prescribing adequate treatment. The number of psychosomatic reactions associated with the intake of certain foods and characterized by the appearance of non-specific symptoms (headache, irritability, depression), as well as food aversion, is increasing at school students in the form of aversion to food on a subconscious level. There are reports of adverse reactions that occur to sugary foods and beverages, various food additives (especially artificial ones). All this requires differential diagnosis of PA and the appointment of adequate therapy aimed at achieving long-term remission and preventing the severe course of the disease [9, 10]. There is a high probability of developing allergic reactions to hidden allergens in foods that the patient does not have or cannot obtain reliable information about. Medicines and cosmetics that contain food allergens as excipients are also dangerous [9, 10]. Therefore, many countries have adopted legislation on the labeling of food and medicines. Currently, 14 food allergens/ antigens are officially designated, which are subject to mandatory declaration. These include albumin, casein, soy, lysozyme, wheat or corn starch, egg, nuts (hazelnuts,

walnuts), peanuts, sesame, lactose, celery, sulfur dioxide, and sulfites [11]. This information helps PA patients avoid allergic reactions to food, medications, or cosmetics.

Thus, new data on potential food allergens will help regulate the frequency of adverse reactions and prevent the development of life-threatening systemic allergic reactions. This will significantly reduce the economic burden on the health care system.

Definition and classification

At the present stage of development, PA is characterized as an adverse (side) reaction associated with a specific immune response of the body to allergenic foods [12]. PA is based on various immune pathological mechanisms: IgE-mediated, non-IgE-dependent (cell -mediated), and mixed forms of immune responses. In this case, various organs and systems are affected: the skin, digestive and respiratory tracts. The pathological process may involve the nervous, endocrine, and cardiovascular systems. Age-related features of the etiological structure and course of clinical manifestations of PA are reflected in the following working classification .

Clinic. Clinical manifestations of food allergy are diverse, since various organs and systems may be involved in the pathological process and multiple organ pathology may occur. For young children, the most characteristic are skin manifestations of food allergies, and among them atopic dermatitis . In this period, it is characterized by the predominance of the exudative form. The first manifestations of the disease usually appear at 2-3 months of life in the form of transient hyperemia in the cheeks. Against the background of hyperemia, small itchy vesicles with serous contents subsequently appear, which are opened with the formation of surface erosions, areas of wetness appear, covered with serous and serous-hemorrhagic crusts. All this clinical picture is accompanied by severe itching. With a localized process, the skin of the face is affected, with the exception of the nasolabial triangle. In a common variant, the process captures the skin of the trunk, the extensor surfaces of the upper and lower extremities. By 1.5-2 years, the exudative form turns into erythematous-squamous. At the same time, the skin becomes dry, itchy papules appear.

The specific diagnosis of food allergies in children is based on the evaluation of the data of the allergological history, clinical picture, results of allergological and laboratory studies. The most significant method of diagnosing food allergies is anamnesis. Allergoanamnesis makes it possible to clarify the spectrum of suspected food allergens, their relationship with the occurrence of certain clinical manifestations, the duration of the time interval between the intake of products and the occurrence of clinical symptoms. Taking into account the possibility of intrauterine sensitization and sensitization through breast milk, the peculiarities of nutrition of pregnant and nursing mothers, the presence of disorders are being clarified in the diet, especially excessive consumption of any food products. It is important to study the nutritional regime of the child: to establish the timing of the introduction of food products (juices, complementary foods), the time of transition to mixed and artificial feeding and compare them with the timing of the appearance of symptoms from the skin or other organs (gastrointestinal tract, respiratory organs, ENT organs), which allows in most cases to identify the "culprit" food product. A food diary can provide significant assistance in identifying causally significant food products. A food diary must be kept constantly for several weeks, noting the days and hours of taking any food, the composition of these products, their quantity, and then in a separate column to record changes in the condition of the child and the time of the appearance of certain signs of the disease. The analysis of the information presented in the diary makes it possible to identify the "guilty" food allergen and, based on this, prescribe a diagnostic elimination diet with the exclusion of the suspected food product. With the correct identification of the allergenic product and its elimination from the

diet, remission of the disease occurs. In addition to anamnesis and diagnostic elimination diet, skin tests (scarification or prick tests) are used in the diagnosis of food allergies. But they are carried out in the period of remission of an allergic disease and only in the allergy clinic under the supervision of an allergist. Their diagnostic significance is assessed in comparison with the anamnesis data. A positive skin test with a food allergen with positive allergoanamnesis data confirms the presence of food sensitization in a child.

Diagnostics

Along with skin tests, laboratory tests are of great importance in the specific diagnosis of food allergies, among them the determination in serum of specific class E immunoglobulins to food allergens by radioimmunological or enzyme immunoassay (1, 3). The use of laboratory tests is preferable in cases where it is impossible to make skin tests (a common skin process, severe or systemic reactions to food products in the anamnesis, long-term use of antihistamines, etc.). The polyclinic of Kazan NIIEM has accumulated considerable experience in laboratory diagnostics of food sensitization in young children. with the use of immunoblotting options (Rida system test, Allergy Scgeep, Allergodip), as well as its own version of allergodiagnostics, combining "battery screening" with the advantages of ELISA, when using liquid biotylated allergens from various manufacturers - "Dr. Fouquet", S.A.R.L.A., "Alkor-Bio". The analyzed data of studies of specific IgE (n=148) in children aged 1 month to 3 years using immunoblot (group 1, n=80) and classical ELISA using biotiled allergens (group 2, n=68) are presented in Table 1. In the spectrum of food sensitization using various test systems, sensitization to milk allergens (97-87.5%) and chicken egg protein (52.541.9%) was the leading one. Sensitization to casein and wheat flour averaged 37.8% to each of the allergens, to allergens of fruits (apple) -18.9%, vegetables (potato) - 18.9%, to soy - 16.2%. In group 1, when using an immunoblot, you there was a higher percentage of sensitization to casein (61.7% in group 1, 19.5% in group 2) and a lower percentage to chicken egg protein (41.9% in group 1; 52.5% in group 2). The level of sensitization to wheat flour in both groups was comparable (35.0-41.1%, respectively). Sensitization to soy and apple was also comparable. The study of the spectrum of sensitization in the age aspect revealed a tendency to decrease sensitivity to cow's milk allergens in the group of children from 1 to 3 years old, chicken egg protein, wheat flour and a significant increase in sensitization to allergens of vegetables ($p<0.05$) and soy ($p<0.05$). In general, there is an impression of comparability of the results of the diagnosis of food sensitization using different diagnostic approaches and test systems, but due to the convenience for practical application, it is preferable to use the option of "battery screening" using biotiled allergens. The significance of a particular food allergen in the realization of the disease can be considered proven if the results of skin tests and/or laboratory tests coincide with the data of anamnesis and the results of diagnostic elimination diets. In doubtful cases, an oral provocative test is performed to confirm the anamnesis data. A positive result of a provocative test with a food allergen is an indication for excluding this product from the child's diet.

Food allergens

The modern allergen database developed by the International Union of Immunological Societies includes more than 400 allergens. Theoretically, any food product can cause an allergic reaction. Food allergens include food products of animal and plant origin, as well as food additives. From the standpoint of modern molecular diagnostics, it is important to determine the components (fractions) of proteins with the highest allergenic properties, responsible for the development of transient (transient) or persistent (long-term) PA, as well as to identify homologous proteins that provide cross-reactivity between various food and non-food proteins. Potential food allergens of animal origin are cow's milk, egg, fish, and seafood [5]. Cow's milk is one of the leading allergens in young children.

Milk contains 30-35 g / l of protein, including whey proteins (α-lactalbumin, β-lactoglobulin) and caseins (as1 -, as2 -, β - and κ-caseins). They have linear and conformational epitopes that have different physicochemical and allergenic properties. Conventional industrial processing does not remove milk proteins. Heat treatment mainly affects the conformational structure of milk proteins (mainly whey), which reduces their allergenicity. Linear epitopes of caseins, on the contrary, thermos.

Revyakinsare stable, and thermal exposure does not affect their allergeni city. In small amounts, milk contains bovine serum albumin - the main allergen of beef, which in its physical and immunological properties is similar to human serum albumin. Allergenic immunoglobulins and lactoferrin are present in cow's milk in small amounts. Determination of allergen -specific IgE antibodies to whole milk protein and its allergenic fractions is of fundamental importance for prescribing personalized diet therapy to patients with allergies to c ow's milk proteins. Identification of individual sensitivity to allergenic fractions of cow's milk protein makes it possible to choose a highly hydrolyzed therapeutic mixture based on the hydrolysis substrate: whey or casein milk. Determination of allergen -specific IgE antibodies to whey proteins and casein is also of great importance for predicting the development and course of (persistent or transient) PA. Thus, according to our data, children with an allergy to milk whey proteins were more likely to develop oral tolerance compared to patients with hypersensitivity to casein (75.0% vs. 33.0%, $p<0.01$). In study S. Yavuz etal. It was shown that children with allergen -specific IgE levels <6 IU/L and the GG genotype of the STAT6 gene went into remission of milk allergy faster than children with allergen -specific IgE levels >6 IU/L and the AA + AG genotype ($p<0.001$) [13]. Therefore, for a more accurate prognosis of the course of PA, a comprehensive determination of the levels of allergen -specific IgEantibodies to milk protein fractions and the study of STAT6 gene polymorphisms are recommended [14, 15].

A common food allergen in young children is chicken egg. It contains 23 proteins, the main major allergens of which are ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotrans ferrin (Gal d 3), egg lysozyme (Gal d 4) and alpha-livetin (Gal d 5). Ovomucoid has the greatest resistance to heating and cleavage by proteolytic enzymes, it is responsible for the development of persistent PA. It was noted that IgE reactions to boiled egg are observed at elevated levels of allergen-specific IgE to ovomucoid [14-17]. Among egg yolk proteins, alpha-livetin is considered the mosthighly allergenic. At the same time, most people with egg allergies tolerate the yolk well. Therefore, when eliminating eggs from the diet, individual sensitivity to its allergenic components should be taken into account. The goal of the diagnosis should be to identify those egg protein components to which the patient has a tolerance. Fish and seafood (shellfish and crustaceans) are a common cause of PA, especially food-borne anaphylaxis. Crustaceans include shrimp, crabs, lobsters, crayfish, lobsters, clams squid, scallops, snails, oysters, mussels. Allergic reactions to fish are persistent, practically do not disappear with age, and tolerance does not develop. The main allergen of fish is parval bumin, and shellfish-tropomyosin. These proteins are highly heat-resistant. This can explain the occurrence of allergic cross-reactions to any fish and to inhaling fumes during cooking. There are rare cases of selective allergy to fish (for example, to one type of fish) [14]. the allergen in chocolate is chitin, which gets into it during the processing of cocoa beans. Less allergenic for the patient is considered bitter chocolate without nuts and dried fruits. It contains 50-95% cocoa beans with minimal concentrations of other additives. Allergic reactions can be caused by certain food additives, including dyes containing proteins:

- annatto (E-160b, bixin, norbixin- - a dye that gives an orange or yellow color to

yoghurts, puddings, cheeses, margarine, butter

- carmine-adye that is added to sausages, canned meat, soft drinks, sweets, lollipops;
- gelatinused in the production of various food products, dosage forms in the form of capsules, in cosmetics, etc. [14].

Adverse reactions to artificial colors (tartrazine), flavor enhancers, and preservatives (glutamates and sulfites) often follow the mechanisms of pseudo-allergic reactions, and they are referred to as food intolerance. They can be caused by mediators (histamine, leukotrienes, prostaglandins, and other cytokines) that are released from allergy target cells in a non - specific way. The development of a pseudoallergic reaction to food is also associated with excessive consumption of foods rich in histamine, tyramine, histaminoliberators or with excessive formation of histamine from the food substrate. An increase in the concentration of histamine in the blood during pseudoallergic reactions can occur with its increased absorption in diseases of the gastrointestinal tract, or increased release of histamine from target cells, or with a violation of its inactivation. Food intolerance can occur due to congenital and acquired ferment pathies. Examples include lactose and fructose intolerance. Most clinical manifestations of food intolerance are difficult to distinguish from true PA. With food intolerance, symptoms appear gradually, persist for a long time, and the results of specific IgE tests are negative [22]. Some people may have psychogenic reactions to food intake. The diagnosis of PA is made based on an analysis of the patient's medical history, medical history, and allergological examination. Diagnostics are performed to identify, confirm, or rule out causal food allergens. An accurate diagnosis of PA is extremely important for selecting a safe and rational elimination diet. In the absence of a diagnosis, it is very difficult to correctly prescribe adequate treatment, assess the risks and prognosis of the development of PA. In addition, the unjustified elimination of many foods with the wrong diet increases the risk of developing deficient conditions, especially proteinand energy deficiency.

Therefore, the diagnosis of PA is based on a complex of clinical and laboratory research methods. Clinical methods include the collection of general and allergic medical history, analysis of medical history, assessment of symptoms of the disease, skin (scarification or Prik-test) and provocative (for strict indications) tests, a trial elimination diet for 7-10 days, and laboratory-determination of the levels of specific IgE antibodies to food allergens using Immulite test systems or Immuno caps that are highly likely to identify the culpable food product. In recent years, the Immuno CAP Solid Phase Allergen method of component (molecular) diagnostics has been actively implemented Phase Allergen Chip (ISAC), which is considered the most informative laboratory method for diagnosing allergies.The chips used in Immuno CAP ISAC are capable of detecting allergen -specific IgE antibodies to causally significant food allergens, as well as cross-reacting with structurally identical allergens of various biological molecules. For example, using this method, it is possible to determine in the patient's blood the major allergen of birch pollen (Bet v 1) and structurally homologous allergenic proteins of alder pollen (Aln g 1), hazelnut (Cor a 1), apple (Mal d 1), peach (Pru p 1), soy (Gly m 4), peanuts (Ara h 8), celery (Apr g 1), carrots (Dau c 1) and kiwifruit (Act d 8). Or patients with an increased level of allergen -specific IgE to milk casein (Bos d8) can simultaneously detect allergen -specific IgE to egg ovomucoid (Gal d1) or peanut Aga h2, to which the patient may develop allergic reactions [14, 22]. When diagnosing PA, it is also necessary to take into account the effects of concomitant diseases and cofactors (physical activity, taking nonsteroidal anti-inflammatory drugs, infections, etc.). During monitoring, the patient is evaluated for the course of the disease (whether tolerance is formed or there is a high risk of severe allergic reaction and/or anaphylaxis

with repeated administration of a causally significant food allergen). It should be remembered that negative results of an allergological examination do not exclude the possibility of illness, and positive ones do not always confirm the diagnosis. Thus, the introduction of new methods of molecular diagnostics increases the possibility of accurate diagnosis of PA and the appointment of personalized diet and pharmacotherapy.

Treating PA is a difficult and complex problem. It requires some knowledge from practitioners and patients themselves. Education of PA patients is one of the main components of complex therapy. This increases adherence to treatment and provides control over the course of the disease. In addition, the patient with PA should carefully read the label of products with the full composition of their ingredients. Currently, in accordance with the legislation of many countries of the world, manufacturers must indicate on the packaging of products 14 major food allergens. In the European Union, in addition to the 8 main allergens, labeling of sesame, celery, mustard, soybeans, sulfur dioxide, and sulfites is mandatory (if the levels of these preservatives are >10 mg / l). At the same time, many foods may contain cow's milk, egg, or nuts without being listed on the product labels. And if you consume only 1 mg of peanuts, 1 mg of egg, 0.02 ml of milk, 5 mg of fish, and 1 mg of mustard, you still have a high risk of developing systemic allergic reactions [1].The main principle of PA treatment is an elimination diet with the exclusion of a causally significant food allergen. The diet is based on an individual plan in accordance with the clinical manifestations of PA, the spectrum of sensitization, age, nutritional status of the child, the functional state of the digestive system, as well as taking into account the previous diet. Currently, personalized diets are prescribed based on the elimination of a specific food allergen and its highly allergenic component. When designing elimination diets, possible cross-reactions to different food groups and allergen groups should be taken into account. Special preventive mixtures based on moderate hydrolysis of milk proteins should be used for feeding infants at risk of developing atopy in the first year of life [1]. Hypoallergenic milk formula intended for allergy prevention should ensure that the child develops tolerance to cow's milk proteins. The allergenicity of the mixture should be reduced, but to a certain level that allows you to save a sufficient amount of so-called tolerogenic peptides. In other words, the depth of protein hydrolysis in the prophylactic mixture should be specially selected. Preventive mixtures for children at risk of developing atopy are necessary for the formation of oral tolerance. Food tolerance can normally be formed in a healthy child when feeding mixtures based on whole protein, since whole protein contains, among other things, peptides of the tolerogenic fraction. Thus, the polymorphism of clinical manifestations and the complexity of the mechanisms of PA development, the heterogeneity of sensitization to various dietary proteins and the unequal response to dietary therapy, as well as the peculiarities of the child's immune response, dictate the need for an individual (personalized) approach to the appointment of dietaryand pharmacotherapy.

Conclusion. food allergy as one of the forms of pathological reactions to food is a fairly common pediatric problem, and the frequency of this pathology in developed countries is growing. The mechanisms of food allergy development are extremely multifactorial and continue to be studied. Studying the role of cytokines allows us to better understand the mechanisms of food intolerance. Due to the identification of the main cells (mast cells, basophils, Th1 and Th2 cells), therapeutic approaches become more effective. The development of these studies will probably allow us to find ways to form food tolerance in patients with food intolerance, thereby complementing the role of elimination diets in their treatment.

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