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THE CURRENT STATE OF THE ISSUE OF THE PREVALENCE AND MOLECULAR DIAGNOSIS OF THE RESPIRATORY ALLERGY SPECTRUM BASED ON MULTIPLEX ANALYSIS (REVIEW)

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ABSTRACT

The aim of the study is to analyze the features of the spread and modern molecular diagnostics of respiratory allergic diseases (AD). **Results and Discussion:** Allergic deseases are among the most common in children, and in recent years there has been a significant increase in frequency, the formation of a more severe progressive course, the presence of combined manifestations with damage to several organs, are considered as a major medical and social problem of modern society. The development of molecular allergology, including the development of recombinant allergens, for accurate diagnosis and effective allergovaccination by allergen-specific immunotherapy (ASIT) is one of the most promising areas in allergology. **Conclusion:** Molecular allergodiagnostics is a diagnosis using recombinant allergens. A recombinant allergen is a purified, cloned, and sequenced allergen source. It is important to use innovative technologies for the diagnosis of patients with allergic diseases using a solid-phase immuno-allergochip, the ImmunoCAP ISAC method.

KEYWORDS: allergic diseases, respiratory allergy, molecular allergy, bronchial asthma, allergic rhinitis.

INTRODUCTION

The frequency of allergic diseases has increased significantly in the last two decades, which is more pronounced in economically developed countries and in countries with unfavorable environmental conditions. According to forecasts, the 21st century will become the century of allergic diseases. Currently, more than 20 thousand allergens are already known, and their number continues to increase.[1,2,4,8,12]

Of particular concern is the steady increase in the prevalence of allergies in children. Early diagnosis of allergic diseases (AD), improvement of treatment and preventive approaches are important issues of modern medicine. The relevance of the problem is determined by the fact that allergic diseases detected in adulthood, as a rule, start in childhood.[3,5,6,7,9,10]

Over the past decades, a significant increase in allergic diseases in both adults and children has been observed worldwide. Today, allergies, which affect more than 150 million people in Europe alone, are a public health problem of pandemic proportions.[6,7,11,13,14]

According to epidemiological studies, AD affects more than 30% of the child population. The total number of patients with allergic diseases – 2013 - 56.3% per 100,000, 2014 - 63.7%. of which: children from 0 to 14 years old 2013 75.2% per 100,000, 2014 92.4%. Children from 15 to 17 years old 2013 70.5%, 2014 - 77.2%. Atopic dermatitis: children under 14 years old 28574.15 -17 years old 2720. Bronchial asthma 2013 - 56.3% per 100,000, 2014 63.7% children from 0 to 14 years old 2013 75.2% per 100,000, 2014 92.4%, children from 15 to 17 years 2013 70.5%, 2014 - 77.2%.[1,5,12,15] According to various authors, the frequency of allergic diseases (bronchial asthma - BA, allergic rhinitis - AR and atopic dermatitis AD) over the past thirty years in many industrialized regions has increased from more than 3.8 to 10 times, both among the adult and child population in all countries of the world.[5,7,10,13]

The prevalence of AD in certain groups is more than 25%, which currently makes it possible to classify allergic pathology as one of the most common diseases of childhood.[1,2,8,9]

According to EAACI (2015), the number of patients with asthma and allergies has reached 65 million and occupy first place in Europe. The number of patients with food allergies amounted to 17 million, which is largely due to environmental imbalance, widespread chemicalization of everyday life and agriculture, widespread and often uncontrolled use of antibiotic therapy, early cessation of breastfeeding and poor nutrition.[10,14] Thus, prevalence rates have significant fluctuations over a wide range,

which, according to researchers, depends on the diagnostic criteria used and methods of epidemiological research. According to domestic and foreign authors, the prevalence of bronchial asthma ranges from 0.2 to 8.1%.[8,12,15,17]

According to summarized data from the ISAAC study (International Study of Asthma and Allergies in Childhood), which is rightfully included in the Guinness Book of Records as the largest study, the frequency of asthma symptoms ranges from 1.0 to 30.8 %. Allergic rhinitis and hay fever in different regions account for 0.2-20%, atopic dermatitis and eczema - 1.6-4.2%.[1,9,10,13,16] The need for the earliest possible detection of allergies and asthma, at stages when there are still few causative factors, does not raise doubts about its relevance and attractiveness for modern researchers.[3,4,15,16]

The aim of the study is to analyze the characteristics of the spread and modern molecular diagnosis of respiratory AD.

RESULTS AND DISCUSSION

According to world statistics, the main forms of atopic diseases - asthma, rhinitis, atopic dermatitis, each individually or in various combinations with each other, in industrialized countries, affect up to 20% of the population.[9,10,12,14] ADs are among the most common in children, and in recent years there has been a significant increase in frequency, the formation of a more severe progressive course, the presence of combined manifestations with damage to several organs, and are considered as a major medical and social problem of modern society.[2,5,8,12] The number of patients with bronchial asthma prevails in childhood. This picture is steadily growing every year.[8,17] So, in this matter, specific anatomical, physiological, and age-related characteristics of the child's body are important; for example, in children under 15 years of age, the upper respiratory tract, as well as the vascular system and gastrointestinal tract, undergo various changes.[6,9]

Consequently, allergic rhinitis (AR) is one of the common ADs, affecting from 10 to 50% of the general population. The total number of patients in the world is more than 600 million people. Its wide prevalence, widespread increase in incidence, negative impact on the quality of life of patients and the cost of therapy define AR as a medical, social and economic problem.[11,13] In Uzbekistan, with its diverse plant and climatic characteristics, a frequently registered allergopathology is respiratory allergy, and hay fever accounts for 185.95 cases per 100,000 population. Dynamics of incidence growth for the period 2007-2014. amounted to an increase of 10.4%. Hay fever is a risk factor for the formation of bronchial asthma (BA) and precedes its development in 32-64% of cases.[13,15] Another pressing problem in our region is another respiratory pathology - asthma, the prevalence of which in Uzbekistan is 4.6 per 1000 population. Globally, the Republic ranks 19th in terms of this indicator.[9,10,13]

According to epidemiological data, from 4 to 10% of the world's population (about 300 million people) suffer from asthma, the most common allergic disease.[11]

It is known that the growing prevalence of AD in the world is influenced by various natural and anthropogenic factors. According to various authors, climate, geographical location, flora, degree of air pollution, urbanization and the level of culture of the population are important. According to. According to WHO, the incidence of asthma is distributed as follows: in Scotland - 18.4%, England - 15.3%, New Zealand - 15.1%, Canada - 14.1%, Brazil - 11.4%, USA - 10.9 %, Russia - 13.9-20%.[1,9,11,15] When studying the quality of life, a high degree of influence of allergic diseases (AD) on the level of emotional, social, and school functioning was revealed, which significantly affects the social adaptation of a child suffering from an allergic disease.[1,5,11,12,18] Thus, the most common allergic diseases are asthma, AR and AD, the early diagnosis of which is also an urgent problem for Uzbekistan, where almost half of the population is children and adolescents. ADs affect the quality of life of children, which significantly affects the child's social adaptation. The most pressing problems of modern allergology are: improving methods for early detection of sensitization at the stages of preclinical manifestations; development of a set of measures to prevent the development of allergic inflammation in people at risk; drawing up personalized treatment and preventive programs to prevent the progression and worsening of the disease; the development of a set of rehabilitation programs aimed at correcting anti-infective immunity is the most pressing issue of modern medicine.[8,9,14,20]

Well, as for modern research methods, it should be noted that at the present stage of development of allergology, the range of laboratory methods available for practical use for identifying a causally significant allergen is quite extensive. All laboratory diagnostic methods to identify the causes of immediate reactions are based on the determination of specific IgE antibodies. Immunoglobulin E (IgE) is a class of immunoglobulins that is normally found in small quantities in blood serum and secretions. IgE was first isolated in the 1960s from the sera of patients with atopy and multiple myeloma. In 1968, WHO identified IgE as an independent class of immunoglobulins. According to WHO, 1 IU/ml (IU is an international unit) corresponds to 2.4 ng. Typically, IgE concentration is expressed in IU/ml or kU/l (kU – kilounit).[5,7,14,20]

Normally, IgE constitutes less than 0.001% of all serum immunoglobulins, according to literary data.[9,13] The structure of IgE is similar to the structure of other immunoglobulins and consists of two heavy and two light polypeptide chains. They are grouped into

complexes called domains.[6,9,15,18] Each domain contains approximately 110 amino acids. IgE has five such domains, unlike IgG, which has only four domains. According to the physicochemical properties, IgE is a glycoprotein with a molecular weight of approximately 190,000 daltons, consisting of 12% carbohydrates. IgE has the shortest lifespan (half-life from blood serum 2 - 3 days), the highest rate of catabolism and the lowest rate of synthesis of all immunoglobulins (2.3 μg/kg per day). IgE is synthesized mainly by plasma cells localized in the mucous membranes.[1,4,8,9,15] The main biological role of IgE is its unique ability to bind to the surface of human mast cells and basophils. According to the literature, it is known that on the surface of one basophil there are approximately 40,000 - 100,000 receptors that bind from 5,000 to 40,000 IgE molecules.[6,14,18] Mast cell and basophil degranulation occurs when two cell membrane-bound IgE molecules bind to an antigen, which in turn triggers sequential events leading to the release of inflammatory mediators.[7,13] In addition to participating in type I (immediate) allergic reactions, IgE takes part in protective anthelminthic immunity, which is due to the existence of cross-linking between IgE and the helminth antigen. The latter penetrates the mucosal membrane and lands on mast cells, causing their degranulation.[2,4,12,18] Inflammatory mediators increase capillary and mucosal permeability, resulting in IgG and leukocytes leaving the bloodstream.[6,14]

A large number of reports are devoted to the peculiarities of interpretation and diagnostic limitations of total IgE.[1,2,7,13] For a practicing physician, it is necessary to know that: approximately 30% of patients with atopic diseases have a total IgE level within the normal range; some patients with bronchial asthma may have increased sensitivity to only one allergen (antigen), as a result of which total IgE may be within normal limits, while the skin test and specific IgE will be positive; the concentration of total IgE in the blood serum also increases in non-atopic conditions (especially with helminthic infestation, some forms of immunodeficiency and bronchopulmonary aspergillosis) with subsequent normalization after appropriate treatment; chronic recurrent urticaria and angioedema are not mandatory indications for determining total IgE, as they are usually non-immune in nature; the normal limits defined for Europeans cannot be applied to representatives of zones endemic for helminthiasis; features of interpretation and diagnostic limitations of specific IgE; the availability of determination of specific IgE should not exaggerate its diagnostic role in the examination of patients with allergies; the detection of allergen-specific IgE (to any allergen or antigen) does not prove that this particular allergen is responsible for the clinical symptoms; the final conclusion and interpretation of laboratory data should be made only after comparison with the clinical picture and data from a detailed allergological history; the absence of specific IgE in peripheral blood serum does not exclude the possibility of the involvement of an IgE-dependent mechanism, since local synthesis of IgE and sensitization of mast cells can occur in the absence of specific IgE in the bloodstream (for example, allergic rhinitis); antibodies of other classes specific for a given allergen, especially the IgG class (IgG4), may cause false negative results; exceptionally high concentrations of total IgE, for example, in individual patients with atopic dermatitis, can give false positive results due to nonspecific binding to the allergen; Identical results for different allergens do not mean they have the same clinical significance, since the ability to bind to IgE may be different for different allergens.[8,12,15,19]

With the development of molecular allergology, the diagnosis of allergies has reached a completely new level, with the ability to quantify sIgE antibodies to individual protein components rather than to whole extracts. Molecular diagnostics (MD), due to its well-founded evidence base and high information content, rightfully occupies one of the leading positions in allergological examination.

In 2016, the European Academy of Allergy and Clinical Immunology (EAACI), in order to popularize molecular diagnostics, published the “Molecular Allergology User's Guide” (MAUG), which provides basic information on molecular allergology, characterizes the main families of proteins, and allergenic molecules, diagnostic options using component diagnostics are described.[8,10]

The development of molecular allergology, including the development of recombinant allergens, for accurate diagnosis and effective allergy vaccination using allergen-specific immunotherapy (ASIT) is one of the most promising areas in allergology.[17,19,20,21] Component diagnostics based on the determination of sIgE to individual protein molecules is an opportunity to increase accurate diagnosis, optimization and prediction of the effectiveness of allergen-specific immunotherapy (ASIT).[5,14,17,21] Component or molecular allergology makes it possible to more accurately determine the nature and cause of cross-activity. In this case, the origin of the allergy is clarified at the component level.[12,14,17,21]

Diagnosing allergies at the molecular level brings clarity to such a complex question - how specific is the allergic reaction in relation to a given source of allergy (birch, peanuts, etc.) or does it come into contact with a homologous element belonging to the same “protein family” , and the allergic reaction induced by it is much weaker. The intensity of the allergic reaction depends on which “protein family” the allergic component belongs to. The most severe reactions (including anaphylaxis) are caused by allergens belonging to the group of so-called storage proteins.[17,18]

Molecular diagnostics used in patients (450) with multiple sensitization allowed resolving controversial diagnostic and clinical situations in 20% of cases.[9,19] The wider practical application of MD is somewhat limited by certain difficulties in interpreting the results of

the examination, which may be due to the indication of nomenclature names of individual molecules, without the names of extracts, familiar and well-known. A doctor who does not have sufficient experience and is unfamiliar with the basics of MD is unlikely to be able to adequately evaluate and interpret the results of molecular analysis, therefore, it is important, along with the use of materials from large-scale studies, to also accumulate practical experience, use practical guidelines on MD, and follow protocols. MD in the hands of an uninformed physician has no advantages over traditional tests, which are more accessible in interpreting the results.[14,17]

Modern diagnosis of allergies involves determining the true trigger of allergic reactions at the molecular level using diagnostic tests based on the use of recombinant or purified natural allergens. More advanced are multiplex chips, which, unlike monocomponent tests, allow one-time determination of a large number of indicators. In this case, the detection of an immune IgE response to specific or cross-reacting components is important. The strategy of a new type of diagnostics - molecular diagnostics of allergies - is based on the identification of sensitization to allergens at the molecular level using natural, highly purified or recombinant allergen molecules, that is, their components, not extracts. Methods for identifying protein components - allergen molecules - can be different, for example, the Dr. Fooke Laboratorien GmbH (Germany) offers molecular diagnostics of allergies in two formats: the ELISA method or the ALFA rapid test, with recombinant and highly purified native allergens, which, using molecular technologies, will increase the accuracy of diagnosis and prediction of the course of allergies. Molecular diagnostics determine objective criteria for prescribing allergen-specific immunotherapy (ASIT) and predict whether prescribing ASIT will be effective or not. ASIT is an expensive treatment method and, as a rule, is carried out over a long period of time (3-5 years), so correct diagnosis, patient selection and identification of the primary sensitizing allergen(s) is important for optimizing the treatment process, including financial points of view.[12,15,17,20,22] MD is a highly informative addition to the individual approach in allergological practice for the purpose of more accurate diagnosis, facilitating more targeted therapeutic and elimination prescriptions. Modern test systems play an important role in three key aspects of component diagnostics.[10,13]

The importance of MD for differentiating cross-reactivity. In the presence of polyvalent sensitization, detected using methods based on identifying IgE sensitivity to extracts, diagnosing true sensitization from cross-reactivity allows diagnosing individual components of allergens - MD. This is how it is possible to identify relevant allergens - inducers, or primary sensitizing molecules, which allows for the optimal selection of ASIT. Thus, molecular diagnostics makes it possible to determine not the source of the allergy, but the causative molecular component, which may be one, but responsible for cross-reactivity, or many different, not closely related ones, responsible for true polysensitization.[6,16]

Thus, according to the literature, there has been progress in the diagnosis of allergies in the world, which is of course associated with a significant breakthrough in molecular biology, immunology, in understanding the etiopathogenesis of allergic diseases, patterns of development and progression of the pathological process. In recent years, increasing attention has been paid to the immunopathogenesis of allergic diseases, especially those that predispose to severe consequences. And of course, their study is fundamental. Despite the widespread coverage of the innovative diagnostic approach in allergology, and the available literature and Internet resources, there is no data on population-based screening studies using various allergy chips. Thanks to information search and analysis of the limited world literature data, it served as the basis for studying the current state of the issue of molecular systematization of respiratory allergy profiles with the possibility of developing a sensitization passport for residents based on multiplex analysis in Uzbekistan.

CONCLUSIONS

Molecular allergy diagnostics are diagnostics using recombinant allergens. A recombinant allergen is a purified, cloned and sequenced allergen source. It is important to use innovative technologies for diagnosing patients with allergic diseases using a solid-phase immuno-allergochip, the ImmunoCAP ISAC method. Thus, ImmunoCAP ISAC is characterized by high accuracy and specificity. The technique is based on immunochemiluminescence; even very low concentrations of IgE antibodies to 112 allergens are detected in a small amount of blood. A review of the literature shows the wide possibilities and advantages of using diagnostics for individual components of allergens. Research results show that 80% of patients have polyvalent sensitization to pollen, food, epidermal and household allergens. Patients with allergic diseases have a high degree of multiple sensitization and severe clinical manifestations, showing the need for accurate molecular and metabolic diagnostics for the prevention of allergic diseases and timely treatment.[18,20] Issues of early detection and prevention of AD, including BA, are important for modern biomedical science and practical medicine. There is primary, secondary and tertiary prevention of bronchial asthma. Primary prevention of asthma is aimed at the occurrence of asthma in healthy people, which consists of preventing the development of allergies and chronic respiratory diseases. An important approach for the prevention of AD is comprehensive screening of the population for early detection of bronchopulmonary and allergic diseases.

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