OVERVIEW OF ALLERGIES WITH FOCUS ON CAUSATIVE AGENTS, CROSS-REACTIVITY, DIAGNOSTIC METHODS AND IMMUNOTHERAPY

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Abstract. *Allergies are exacerbated immune responses of the body to certain structures, called allergens, which under normal conditions do not elicit any response from the body. Cross-reactivity is a phenomenon that reveals the phylogenetic relationship between allergens and is important to consider when starting a diagnostic investigation in order to determine the best route of immunotherapy. The most commonly used methods to asset allergies are: skin prick test, component-resolved diagnosis, immunoglobulin E measurement assay, basophil activation test and challenge tests. Immunotherapy, unlike pharmacotherapy, induces tolerance to certain allergens, even after the completion of treatments, altering the natural course of the pathology. In terms of allergy diagnosis, the main problem is outlined around the quality of allergen extracts. Besides the fact that allergen extracts may have other immunogenic components that are not directly related to the targeted allergy, there are also panallergens in nature that can introduce errors in the diagnosis of some allergies. So the main efforts in this direction are done for the development of purified allergen extracts. In this review we have classified and described allergies based on the causative agent into: pollen allergy, food allergy, dust mite allergy, fungal allergy, insect allergy, pet dander allergy and drug allergy.*

Keywords*: allergy, cross-reactivity, immunotherapy, allergy diagnostic methods*

INTRODUCTION

An allergic reaction is an exacerbated response to a stimulus (called an allergen) that under normal conditions would not cause a response from the body. The basic mechanism underlying the allergic reaction is common to all allergens. Allergens can enter the body via various pathways where they are taken up and processed by antigen-presenting cells prior to CD4 T lymphocytes exposure. This process results in the generation of Th2 lymphocytes which will produce interleukins (IL-4, IL-13). Subsequently, B lymphocytes are activated and immunoglobulins E are produced (IgE). When a second exposure to the same antigen occurs, mast cells and basophils are activated and then release inflammatory mediators such as histamines, leukotrienes and prostaglandins through the process of degranulation. Allergy symptoms can occur directly at the site of contact with allergens or can affect other areas (SATHE et al., 2016).

Cross-reactivity reflects a phylogenetic relationship between organisms. The basis of cross-reactivity is based on immunological recognition. Two allergens are cross-reactive if there is a single antibody (or LT receptor) that reacts with both. (AALBERSE et al, 2001). There are several families of great interest for the study of cross-reactivity, among them are mentioned: profilins; non-specific lipid transfer proteins; avian proteins; mammalian-associated proteins- utmost studied being milk proteins such as alpha-lactalbumin, beta-lactoglobulin and casein; polcalicins- restricted to pollen (HAUSER et al., 2008).

The ability to alter the natural course of a disease differentiates immunotherapy from other treatment methods. Pharmacotherapy using antihistamines, corticosteroids and

bronchodilators reduces symptoms but does not prevent progression of the disease. Another aspect that differentiates immunotherapy from pharmacotherapy is that immunotherapy has the ability to induce pathological remission even after the completion of the treatment (PENAGOS, 2018).

KUCUKSEZER et al. (2020) identify the main routes of administration of immunotherapy with the following advantages and limitations: subcutaneous immunotherapy- with proven efficacy and safety, possible applications for venom reaction, limitations are related to undesirability of repeated injections, dependence on medical facilities for administration, long duration of administration, severe risks of hypersensitivity; sublingual immunotherapy- proven efficacy and safety, no inconvenience of injections, preferred by children, less dependent on medical facilities, potentially administered from the comfort of one's own home, main limitation is related to lower efficacy compared to subcutaneous immunotherapy; oral immunotherapy- has curative potential for food allergies but limitations related to safety of administration and efficacy are very prominent; intralymphatic immunotherapy- main advantage is related to duration of treatment but there are limitations to possible adverse reactions and constant dependence on medical facilities; epicutaneous immunotherapy- has wide applicability for aeroallergens and food allergens, has a good safety profile, shows promising results, limitations are related to possible adverse reactions.

In terms of allergy diagnosis, the main problem is outlined around the quality of allergen extracts. Besides the fact that allergen extracts may have other immunogenic components that are not directly related to the targeted allergy, there are also panallergens in nature that can introduce errors in the diagnosis of some allergies. So the main efforts in this direction are done for the development of purified allergen extracts.

In this article we have classified and described allergies in terms of cross-reactivity, diagnostic methods and immunotherapy, depending on the causative agents as it follows: pollen allergy, food allergy, dust mite allergy, fungal allergy, insect allergy, pet dander allergy and drug allergy.

POLLEN ALLERGY

Pollen allergy is considered a major health problem that can massively influence patients' quality of life. Submicron particles from pollen can penetrate deeper into the airways leading to asthma, obstructive lung disease and other allergic reactions. Climate and air pollution levels can affect the concentration of the airborne pollen (RAVINDRA et al., 2022).

Allergy-causing pollen generally comes from three main groups of plants: trees, grasses and weeds. Allergy patients may be sensitive to one or more taxa. Panallergens in plant pollen can sensitise the human immune system and contribute to the development of reactions to several other allergens (WESTMAN et al., 2020).

Cross-reactivity

The association between food and pollen is based on structural similarities of the allergens involved in the allergic reaction. The most common associated allergies are the following: birch/olive/plane tree pollen with apples, cherries, nectarines, carrots, peanuts, potatoes. Pollen sensitivity often precedes food allergies (PONCET et al. 2020).

Immunotherapy

Nowadays long-term tolerance to inhalant allergens could only be achieved by immunotherapy with standardised, whole extracts administered subcutaneously or sublingually. These attempts include combining allergens with monoclonal antibodies directed against LTh2 or other immunological constructs such as toll like receptorst (TLR) antagonists. Another

approach may be related to passive immunotherapy by direct injection of immunoglobulin G4 (IgG4) that are directed against IgE (DURHAM & SHAMJI, 2023).

Diagnostic methods

Skin prick test (SPT) is the most common method used in doctors' offices to diagnose pollen allergy and is based on the use of raw pollen extracts, in addition to SPT tests on crude pollen extracts, such tests have also been developed for profilins and lipid-transfer proteins, which are some of the world's best-known panallergens; the basophil activation test (BAT) is a newer method of allergy testing and involves monitoring the response of basophils by activating markers CD63 and CD203 or by monitoring the mediators released, such as histamines or beta-haxosaminidases, to passive stimulation of basophils; quantitative measurement of specific serum IgE (sIgE) assay can be done either by singleplex or multiplex assays, both of which are accessible and used in current practice (PABLOS et al., 2016; BARBER et al., 2015).

FOOD ALLERGY

Any food can cause an allergy, however, some foods such as shellfish, eggs, fish, milk, peanuts, soy, tree nuts and wheat cause the majority of allergic reactions (about 90%) (LEHRER et al., 2002).

Cross-reactivity

Considering food allergies, there is a phenomenon known as "pollen-fruit syndrome" which involves the generation of food allergies via the respiratory tract. The exhaustively studied case is related to pollen of Betulaceae and Fagaceae which are cross-reactive with a wide range of commonly consumed foods such as vegetables and fruits (SCALA et al., 2023).

Cross-reactivity to foods can occur within the same food classes, e.g. pecan-nut, cashew-pistachio, wheat and rye (KAZATSKY & WOOD, 2016).

Immunotherapy

Recently, the focus for treating allergies has been directed towards areas such as immunotherapy and monoclonal antibody therapy (HWANG et al., 2022). In terms of monoclonal antibodies, omalizumab is an effective treatment for food allergy. The use of this monoclonal antibody, allows desensitization at a faster rate and tolerance of a higher dose of food but unfortunately not in a sustained manner (HUMBERT et al., 2014).

Diagnostic methods

Skin prick rest is commonly used for food allergy, although false negative results can occur if the allergens of interest are not found in sufficient quantities, also a modified version of this test is available where fresh foods (especially fruit and vegetables) are used instead of standardised extracts; component resolved diagnostic (CRD) unlike conventional methods that measure the total amount of IgE in whole food extracts, CRD (mollecular allergen analysis) identifies IgE specific to a single protein in a food, which leads to a massive increase in the accuracy of the result; BAT- has generally comparable results in sensitivity to SPT or sIgE but much improved in specificity; oral food challenge is the clearest method for food allergy testing, but it should only be performed by medical personnel and the doses should be increased gradually to avoid anaphylactic shock. (GUPTA et al., 2018; GOMES-BELO et al., 2018).

DUST MITE ALLERGY

Exposure to dust mites is one of the most common causes of allergy worldwide. *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* are the most common allergy-causing mites in the human population and are widespread worldwide. Due to their

cosmopolitan status, the mites have even been detected on submarines and space stations (MILLER, 2019).

Cross-reactivity

Cross-reactivity has been reported between mites and crustaceans (shrimps, crabs, crayfish) and insects (cockroaches, grasshoppers) but also molluscs (snails, clams and squid), with symptoms of varying intensity but which can reach eventually to anaphylaxis. Tropomyosin (Der p10) is considered the panallergen incriminated for this phenomenon (MILLER, 2019). Chitin, present in insects, crustaceans, fungi and intestinal parasitic worms, is also present in the exoskeleton of mites and activates the innate immune system via the pattern recognition receptors, including TLR2 and lectin C-type, thereby inducing Th2 lymphocyte mediated responses (KIM et al., 2015).

Immunotherapy

Clinically, raw protein extract from mites is commonly used for densensitization, but due to the complexity and difficulty of standardizing this type of extract, the desensitization process involves many adverse reactions such as urticaria, rhinitis, asthma and even anaphylaxis (ZIMMER et al., 2017). Vaccines for the prevention and treatment of mite allergy can be obtained by several methods: purified proteins produced via biotechnology in model organisms such as *Escherichia coli* or yeasts; epitopes derived from T-cells; hypoallergenic vaccines that eliminate the IgE-mediated response (CAO & LIU, 2020).

Diagnostic methods

SPT- but with the possibility of false negative results if antihistamines are used and false positive results if the skin being tested is eczematous or with dermatographism, also the results are depending on the quality of the allergen extract; provocation tests- used at nasal, bronchial or conjunctival level, it is recommended before this tests not to use drugs such as antihistamines, antidepressants and corticosteroids; serological tests- measurement of the concentration of specific IgE, here being necessary to take into account the fact that mite extracts generally contain the Der p 1 and Der p 2 fractions but in varying amounts; microarray-based test- the advantage of these tests is that several allergens from different sources can be tested at the same time; molecular diagnosis CRD- differential diagnosis, based on standardised immunogenic fractions, with the disadvantage that only one fraction can be tested at a time; BAT- can be performed even under antihistamine treatment, unlike SPT. (BREHLER, 2023; HUANG et al., 2023).

FUNGI ALLERGY

Exposure to fungal components (both indoors and outdoors), including spores, is a trigger for respiratory allergies and asthma as well as for atopic dermatitis (CRAMERI et al., 2014). The genera most commonly incriminated for generating allergic reactions are: Alternaria, Aspergillus and Cladosporium (CRAMERI et al., 2006).

Cross-reactivity

Cross-reactivity between genera has been demonstrated for fungi. IgE produced by *Candida albicans* can cross-react with species of the genus Malassezia, with polysaccharides of the species *Saccharomyces cerevisiae* and with other species of the genus Candida, resulting in increased total IgE in patients with atopic dermatitis (THAMMAHONG et al., 2020).

Immunotherapy

As a treatment for fungal allergies, the most stable and successful treatment is to avoid exposure to allergens, but given the ubiquitous nature of fungi this, although desirable, is relatively impossible. In terms of immunotherapy there are huge gaps due to the lack of standardised fungal extracts (PFEIFFER & SWOBODA, 2023). The lack of these extracts is caused

by multiple factors such as: dependence of the generation of fungal compounds capable of triggering IgE production on mycelial growth, instability of extracts due to protease content, culture conditions for fungi, extraction procedures (TWAROCH et al., 2015).

Diagnostic methods

Diagnostic methods for fungal allergy have not been standardised and therefore the usual methods are used: SPT-with whole extracts from moulds; serological tests- for specific antibodies to certain moulds; conjunctival challenge test- administered as eyedrops (TORRES-RODRÍGUEZ et al., 2012; FUKUTOMI & TANIGUCHI, 2015).

INSECT ALLERGY

Hymenoptera venom allergy is a classical IgE-mediated allergy caused by IgE interaction with receptors on the surface of mast cells and basophils. Hymenoptera venom allergy is one of the most severe hypersensitivity reactions, with a high potential for anaphylaxis (BILO et al., 2005). Reactions that may occur following venom injection are: local, regional, systemic, anaphylactic or delayed hypersensitivity reactions. Bee, wasp and ant venoms induce IgE-mediated hypersensitivity reactions, type I or III, involving both immune complexes and complement activation (KAUSAR, 2018).

As the world's population has grown, so has the demand for food. Insects can be a quite suitable alternative for providing protein intake (MLCEK et al., 2014). DE GIER & VERHOECKX (2018) list the following taxa as the most consumed worldwide, according to the Food and Agriculture Organization: Coleoptera (31%), Lepidoptera (18%), Hymenoptera (14%), Orthoptera (13%), Hemiptera (10%), Isoptera (3), Odonata (3%), Diptera(2%).

Cockroaches are very well studied insects as a source of allergens. Although there are many species of cockroaches associated with allergies, most studies focus on the following species: *Blatella germanica*, *Periplaneta americana* (FUKUTOMI & KAWAKAMI, 2021).

Cross-reactivity

The most important insect-associated panallergen is tropomyosin. This is a protein with an alpha-helical structure. The most important sources of tropomyosin as a food allergen are crustaceans, molluscs, cephalopods, parasitic nematodes. Cockroaches and mites are described as respiratory sources of tropomyosin. Arginine kinase is another important panallergen with a highly conserved structure in the invertebrate lineage (DE MARCHI et al., 2021).

Immunotherapy

For individuals who experience anaphylactic shock to hymenoptera venom the only effective treatment in case of future exposure is immunotherapy. In particular immunotherapy associated with hymenoptera venom allergy has a very high success rate, from 75% to even 98% chance of protection from a subsequent reaction (OLLERT & BLANK, 2015).

Diagnostic methods

SPT; serologic tests- to specific antibodies; CRD- and since insect allergens are highly cross-reactive allergens due to the fact that they are a cocktail of immunogenic and non-immunogenic fractions, CRD may be the best way to screen for the presence of allergy; BAT- is more sensitive than intradermal tests; indirect tests- measuring serum tryptase levels can be a risk indicator in people with insect allergy (GOLDEN, 2014; DE GIER & VERHOECKX, 2018).

PET DANDER ALLERGY

Among other allergens, those from animals, especially dogs and cats, can lead to sensitisation and this can be a issue, especially as the number of pet owners is increasing. People with atopic dermatitis who are also sensitised to animals have a much higher risk of

developing allergic diseases of the respiratory system (CHU et al., 2020). The domestic cat (*Felis domesticus*) and domestic dog (*Canis lupus familiaris*) are carnivorous mammals, highly valued for their companionship but are the animals most commonly implicated in allergic diseases (REYNOLDS & FINLAY, 2017).

Cross-reactivity

The following antigens have relevance in animal allergy-associated cross-reactivity as they show a high degree of homology: uteroglobins, arginine esterases, laterins, cystatins, lipocalins, serum albumin, immunoglobulins, epididymal secretory protein E1 (HEMMER, 2023).

Immunotherapy

In a review of 60 articles, SMITH & COOP (2016) conclude that there is insufficient data to confirm the efficacy of immunotherapy using dog allergen extracts. Currently the most common modalities of intervention in immunotherapy for animal allergy are subcutaneous therapy and sublingual therapy. This type of therapy has significant results especially as a complement to alternative therapies (VIRTANEN, 2018).

Diagnostic methods

Molecular diagnosis including CRD; SPT; challenge tests used only in patients with negative SPT and SIgE results (CHAN & LEUNG, 2018; KOZLOV et al., 2023)

DRUG ALLERGY

Adverse reactions to medicinal products fall into two broad categories: type A and type B. Type A reactions are predictable, dose-dependent, rational and due to pharmacological characteristics. Type B reactions are unpredictable, irrational, dose-independent and not due to pharmacological properties. Drug allergy belongs to category B (PICHLER & HAUSMANN, 2017).

According to WARRINGTON et al. (2018) the most common drugs that can cause allergy are: penicillin, cephalosporins, sulphonamides, contrast agents, local anaesthetics, systemic anaesthetics, acetyl salicylic acid/non-steroidal anti-inflammatory drugs, monoclonal antibodies.

Cross-reactivity

Considering drugs, cross-reactivity is found between different classes of drugs or within the same type of drugs. It is very important to distinguish here between LT or LB mediated cross-reactivity, as LT can recognise even the core of the drug (DEPTA & PICHLER, 2003). According to ROMANO et al. (2005) the following drugs are frequently implicated in cross-reactivity phenomena: beta-lactam antibiotics, non-beta lactam antibiotics such as sulfonamides and quinolones, muscle relaxants, hypnotics, anticonvulsants, heparins, contrast agents, corticosteroids,

Diagnostic methods

SPT- validated only for penicillin; patch testing; intradermal testing; drug challenge- generally start with sub-therapeutic doses to avoid anaphylaxis; indirect tests- determination of tryptase, histamine and leukotriene concentration; serological tests- SIgE, FEIA- fluorimetric enzyme immuno assay- in which drug is covalently bound to poly-L-lysine, not available for many drugs; RAST; ELISA; BAT (ABRAMS & KHAN, 2018; SARETTA et al., 2023)

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