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PERSPECTIVES ON THE CORRELATION OF RESPIRATORY AND FOOD ALLERGY-ORAL ALLERGY SYNDROME

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ABSTRACT
The increased prevalence of allergic disorders is a major global public health problem. The common indicator of atopic dysfunctions is the production of specific IgE (sIgE) against allergens. Cross-reactive allergic reactivity occurs when IgE antibodies initially recognized as epitopes of an allergic reaction are identified as causing similar problems in another allergy. Component-based diagnosis using microarray technology has recently been introduced into allergy practice. Patients who are polysensitized or have unclear sensitization patterns are candidates for evaluation using molecular allergy.
KEY WORDS: *pollen allergy, food allergy, oral allergy syndrome.*

INTRODUCTION

Allergies are heightened immune responses triggered by specific substances, known as allergens, which are normally harmless to the body. Cross-reactivity, a phenomenon that highlights the phylogenetic relationships between allergens, plays a crucial role in guiding diagnostic investigations and determining the most effective approach to immunotherapy (Ciobanu & Ianovici, 2024).

The increased prevalence of allergic disorders is a major global public health problem (Milwaukee, 2011). In the United States of America, millions of people are affected by IgE-mediated conditions, which not only alter the quality of life but also add economic burdens to both patients and society (Meltzer et al., 2009; Ebert & Pillsbury, 2004; Salo et al, 2014). Allergies are widespread in Europe also, being estimated that 40% of the population has an allergic condition linked to pollen (Leru et al., 2015). In recent decades, there has been growing concern about air pollution, which is caused not only by physical and chemical pollutants but also by fungal spores and pollen grains. Certain types of spores are of particular clinical significance because they are considered allergens (Ianovici, 2020).

The common indicator of atopic dysfunctions is the production of specific IgE antibodies (sIgE) against allergens. Studies on specific IgE antibodies using *in vivo* skin tests or *in vitro* serological analyses confirm allergic sensitization, while the patient's clinical history and physical examination remain important foundations in diagnosing allergic disorders (Hamilton, 2010). Monitoring the prevalence and sensitization patterns mediated by IgE in populations over time is important because allergic sensitization is a major risk factor in the development of allergic disorders (Milwaukee, 2011). When it comes to the immune system and the medical conditions associated with it, it is very important to consider the psychosocial factors withal. For example, elevated cortisol levels caused by stress can affect the overall function of the central nervous system, leading to immune imbalance and the instalation of atopy (Ianovici & Batalu, 2023; Batalu & Ianovici, 2018).

Diagnosing and managing food allergies are complicated by an abundance of homologous, cross-reactive proteins in edible foods and aeroallergens. This leads to allergic sensitization of patients (positive tests) to many biologically related foods. However, many patients are sensitized to foods without presenting clinical reactivity (Cox et al., 2021). The main cross-reactive relation regarding food is with aeroallergens, mainly pollen. Aeroallergens are more common natural allergens that can penentrate into the body mucosa (nasal, eyes, oral and lungs) and can lead to allergic reactions (Ianovici, 2007).

1. Cross-reactivity and Oral Allergy Syndrome (OAS)

Cross-reactive allergic reactivity is defined by the situation where IgE antibodies originally recognized as epitopes of one allergic reaction are identified causing similar issues in another allergic reaction. More than 65% of food allergens consist of only four basic species: *Bet v 1* (major allergen of birch pollen) homologs, profilins, cereal prolamin superfamily, and cupins. This could indicate broad cross-reactivity of IgE, even among allergens that appear in systematically distinct plants (Muluk & Cingi, 2018). IgE cross-reactivity can manifest clinically or be irrelevant. The overall sequence identity of surface structures is a major determinant of cross-reactivity, and a sequence identity of 35% has been suggested as a cut-off for potential cross-reactivity (Goodman et al., 2005). The most common cross reactivity directions are hightlighted in table 1.

TABLE 1. The main cross reactivity directions

Allergen type	Cross-reactivity	Reference
Pollen	-among different types of pollen. -with food (e.g. birch-apple). -with latex.	Sharma & Vitte, 2024
Food	-among different types of food (e.g. fish, nuts). -with pollen.	Sandip et al., 2023
Fungi	-among different types of fungi. -with food (e.g. fungus-related food such as mycoproteins and fermented foods).	Xing et al., 2022
Insects	-with food (e.g. seafood) -with house dust mites.	Eischeid et al., 2023 Cunha et al., 2023
house dust mites	-with food (e.g. seafood). -with other invertebrates (e.g. helminths).	Lisboa et al., 2024
Drugs	-among different types of drugs (e.g. penicillin-cephalosporins).	Romano et al., 2018
pet dander	-between animal species (e.g. dog-cat).	Liang et al., 2024

Oral Allergy Syndrome (OAS), also known as "pollen-food allergy syndrome", is a type of food allergy limited to the oral mucosa and caused by unprocessed fruits, raw vegetables, and nuts (Ta et al, 2015). The most well-known symptom is irritation in the oral cavity and throat, which occurs immediately after the food touches the oral cavity and typically continues for only a few minutes after the food is swallowed. OAS occurs in individuals with pollen allergies and is triggered by allergens in nuts, vegetables, and fruits that are fundamentally similar to pollen allergens. Symptoms can occur with a single food or a wide range of fruits and vegetables. For example, a single fruit, such as an apple, can trigger symptoms. In OAS, patients react to various foods. For example, for patients sensitized to birch pollen (an airborne allergen causing frequent reactions in the spring), fruits with seeds or carrots can cause an allergic reaction. Additionally, in subjects with birch pollen allergy, peanuts, almonds, and hazelnuts can cause itching in the mouth. Individuals with ragweed allergy may have OAS when consuming melon, cucumber, banana, or zucchini (Muluk & Cingi, 2018).

A probable association between pollen allergy and food sensitivity has been established. The production of specific IgE directed against common cross-reactive structures (panallergens), shared by pollen and plant-derived foods, is the most plausible theory (Caballero et al., 1998). Pollen appears to be the primary source of sensitization.

Regarding plant-food allergens, the most studied allergen-specific protein family includes nonspecific lipid transfer proteins (nsLTPs), the pathogen-associated protein family (PR-10 proteins), profilins, storage proteins (2S albumins, 7S/11S globulins), and cross-reactive carbohydrate determinants (CCDs).

1.1. NdLTPs

NdLTPs are small molecules, about 9-10 kDa in size, that facilitate the transport of phospholipids and galactolipids across membranes. As panallergens, they have ubiquitous distribution in the tissues of many plant species, resulting in relevant cross-reactivity between fruits and vegetables, including apples, cherries, sweet chestnuts, cabbage (with 50% identity to nsLTPs from peaches), nuts, lettuce, and hazelnuts (Hoffmann-Sommergruber & Mills, 2009). Grapes and wine, which have also caused oral allergy syndrome in patients, may contain nsLTP homologs and cross-reactive nsLTPs with those from peaches (Pastorello et al., 2003). They demonstrate increased stability and are highly resistant to pepsin and heat treatment. Allergic symptoms involving nsLTPs are more likely to be systemic and severe, in addition to inducing OAS (Vieira et al, 2012).

Given the high frequency of *Parietaria pollinosis* in the Mediterranean area, this sensitization has been described, though rarely, only in association with pistachio sensitization (Liccardi et al., 1996; Liccardi et al., 1999). Conversely, *Artemisia* sensitization has been implicated in several pollen-food syndromes with varying frequencies, in different food families: celery, carrot, parsley, and caraway, fennel seeds, and coriander (*Apiaceae*), bell pepper (*Cruciferaceae*), hot pepper (*Piperaceae*), mango (*Anacardiaceae*), garlic, onion, and leek (*Liliaceae*), mustard, broccoli, and cabbage (*Cruciferae*), peanut *(Leguminosae*), almonds, and peaches (*Rosaceae*) and chamomile infusion (*Asteraceae)* (Egger et al., 2006). However, *Art v 3* (nonspecific lipid transfer protein from *Artemisia vulgaris* pollen) can be positive without sensitization to other nsLTPs (Gadermaier et al., 2009), and there is a low probability of cross-reactivity between *Par j 2* (major allergen of *Parietaria judaica* pollen) and other nsLTPs (Ciardiello et al., 2010).

1.2. Profilins

Profilins are small proteins (12-15 kDa) that act as actin-binding proteins and can play a key role in regulating intracellular transport processes, morphogenesis, and cell division. Profilins are minor allergens, highly cross-reactive even between distantly related species, including latex, thus increasing the risk of multiple pollen-food sensitizations, not always clinically relevant (Hoffmann-Sommergruber & Mills, 2009). Presenting symptoms of citrus, melon, banana, and/or tomato have been described as clinical indicators of profilin sensitization. Their prevalence in pollen-allergic patients in Central and Southern Europe is estimated to be 10-35% and rarer in the northern part of the continent (Asero et al., 2008). This rate increases to 55% in the population of

patients with multiple pollen sensitizations, where grass sensitization is dominant (Valenta et al., 1991). Exposed to heat treatment, irradiation, or very high pressure, the IgE-binding activity is not affected. Symptoms range from mild to severe, causing OAS as the main clinical manifestation of food allergies (Vieira et al, 2012).

1.3. PR-10

The first allergen identified from the PR-10 protein family was the allergen from birch pollen (*Betula verrucosa*), *Bet v 1*. In regions where trees are rare or absent, a positive test for this pollen often reflects sensitization to *Bet v 1* homologs (PR-10) from other closely related trees or sensitization to other pollen allergens, such as profilins (*Bet v 2* homologs) from grasses. Food reactions observed in birch-allergic patients are explained by specific IgE antibodies to *Bet v 1*, induced by birch pollen. Between 50 and 90% of patients allergic to this pollen type reported the presence of associated pollen-food allergies (Menz et al., 1996). PR-10 proteins are mainly located in the fruit pulp. Symptoms are usually mild and restricted to the oral cavity, summing up as OAS. In general, PR-10 proteins are labile to pH changes and have intermediate resistance to heat treatment.

2. ***Determination of Cross-Reactive Allergies***

2.1. ***Microarray Technique***

Component-based diagnosis using microarray technology has recently been introduced into allergy practice. IgE-mediated allergy diagnosis is based on skin testing and is supported by standard *in vitro* testing for specific IgE. These traditional diagnostic methods use natural allergen extracts, which contain a mixture of allergenic and non-allergenic molecules that are difficult to standardize, mainly defining the source but not the allergenic molecule(s) that caused sensitization (Vieira et al, 2012).

Quantitative measurements of specific IgEs for single allergen components are now available. This component-based diagnosis is based on natural or recombinant allergens with structural and immunobiological properties comparable to natural sources, outlining a detailed IgE reactivity profile for each patient (Valenta et al., 1999). Using the microarray technique, sensitivity to multiple allergenic components (natural, purified, or recombinant allergens) is determined from the same serum sample (Lucas, 2010).

In diagnosing suspected food allergies, skin tests with conventional extracts have low specificity and low allergenic potency (EEACI Subcommittee, 1993; Sampson, 2002). Using fresh foods is an alternative, but it presents reproducibility problems

(Ortolani et al., 1989) and an increased risk of adverse reactions, including anaphylaxis, especially in children (Devenney et al., 2000; Liccardi, 2006). Food challenges are the only method to manage adverse reactions to a food. However, these procedures are not fully developed, and there is no agreement on standardized procedures (Asero et al., 2007). Moreover, all these methods must be performed in a safe environment and only by doctors with appropriate training in allergy. Among all *in vitro* methods, determining specific IgE with whole extracts has low specificity (Lucas, 2010; Sampson, 2002). Purified natural or recombinant allergens have proven useful by overcoming the mentioned limitations (Valenta et al., 1999; Vieths et al., 2001).

Biological cross-reactivity can be an important but not exclusive factor in grouping specific allergen IgE. Studies on microarray-based IgE detection in polysensitized allergic patients, suspected of food allergy, concluded that the possibility of performing multiple IgE measurements with single protein allergens, especially using the microarray technique, is a useful, simple, and non-invasive diagnostic component for complex polysensitized allergic patients (Vieira et al., 2011).

2.2. ISAC Tests

Recombinant proteins can be used to determine the specific food components that lead to patient sensitization. The World Allergy Organization considers molecular allergy diagnosis suitable for patients whose clinical cases and IgE-based tests are inconclusive. Molecular allergies are useful in selecting immunotherapy. Patients who are polysensitized or present unclear sensitization patterns are candidates for evaluation using molecular allergy (Canonica et al, 2013). Moreover, cross-reactivity is easily identified in patients sensitized to components with similar epitopes. The multiplex platform for molecular allergy diagnosis currently used in medical practice is the ImmunoCAP ISAC-Immuno-Solid phase Allergen Chip (Thermo Fisher Scientific/Phadia AB), consisting of a biochip containing 112 different allergens from 51 different sources (including foods, pollen, and animals), fixed on a microarray that allows the semi-quantitative determination of specific IgE antibodies (Westwood et al, 2016; Hamilton et al, 2015; Maesa et al., 2021).

ISAC tests have numerous advantages, considering that they are safe tests and available even for allergists who do not work in a hospital setting, facilitating diagnosis in children and patients at risk of systemic symptoms (Goikoetxea et al., 2010; Vieths et al., 2001). The lower amount of serum required facilitates the use of the technique in pediatric patients. Moreover, ISAC accuracy has been validated in terms of correlation

with standard routine tests and similar potency in terms of allergen unit mass (Jahn-Schmid et al., 2003; Wöhrl et al., 2006).

3. ***Discussions***

Diagnosing allergies in polysensitized adult and pediatric patients needs to be improved to clarify the nature and cause of allergic reactions and to promote effective methods of managing disorders (Lucas, 2010; EAACI Subcommittee on Skin Tests, 1993). Food allergies in patients sensitized to aeroallergens are an example where the relevant issue raised is identifying patients at high risk of developing systemic reactions (Vieira et al., 2011).

Being an IgE-mediated allergic reaction that typically occurs in response to fresh fruits, vegetables, and nuts, OAS arises due to cross-reactivity between pollen allergens and structurally similar proteins found in these foods. Given that the condition is often underrecognized, there are limited studies addressing its prevalence, etiology, pathogenesis, and treatment (Kelava et al, 2014).

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