

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

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ABSTRACT

Allergic disorders are a major health concern, notable by their expanding prevalence. Production of specific immunoglobulins E is the main marker of allergic sensitization. Cross-reactive allergic reactivity occurs when IgE antibodies, initially considered as specific for one type of allergic dysfunction, are identified as causing similar reactions in another allergy. Component-based diagnosis using microarray technology is a newly introduced technique for detecting allergies. The cases of polysensitization or uncertain allergy patterns are evaluated by the molecular allergy technology.

KEY WORDS: *cross-reactivity, oral allergy syndrome, food allergy, pollen allergy.*

INTRODUCTION

Allergies are heightened immune responses triggered by specific substances, known as allergens, which are normally harmless to the organism. Different allergens can be so similar that the immune system mistakes one for another. The phenomenon that indicates how closely related those allergens are is named cross-reactivity. Cross-reactivity plays a crucial role in guiding diagnostic investigations and determining the most effective approach to immunotherapy (Ciobanu & Ianovici, 2024).

Allergic disorders are a major health concern, notable by their expanding prevalence (Milwaukee, 2011). In the United States of America, more than 50 million people suffer by IgE-mediated conditions that negatively impacts the life quality and economical situation of both the patients and the society (Meltzer *et al.*, 2009; Ebert & Pillsbury, 2004; Salo *et al.*, 2014). Allergies are also widespread in Europe: the estimation is that approximately 40% of the population is sensitized to pollen allergens (Leru *et al.*, 2015). In the last decades, air pollution is of great concern, being additionally caused by pollen grains, fungal spores, and not only by physical and chemical pollutants.

Certain types of spores are of particular clinical significance because they are considered allergens (Ianovici, 2020).

Production of specific immunoglobulines E is the main marker of allergic sensitization. Although the clinical image and physical consultation are fundamental for detecting allergies, in vivo and in vitro tests for detecting specific IgE antibodies are also helpful in diagnostics (Hamilton, 2010). Allergic sensitization is highly associated with the development of various allergic disorders. Therefore, an important clinical step for increasing patients' life quality is screening the IgE mediated patterns and the prevalence of sensitization over time (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 CNS (central nervous system), leading to both atopy and immunological imbalance (Ianovici & Batalu, 2023; Batalu & Ianovici, 2018).

The challenge in diagnosing and afterwards managing food allergies is identifying the cross-reactive, homologous proteins in both food and aeroallergens, which lead to allergic sensitization of patients to related foods (Cox *et al*, 2021). The main cross-reactive relation regarding food is with aeroallergens, mainly pollen. Aeroallergens are more common natural allergens that can penetrate 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 occurs when IgE antibodies, initially considered specific for one type of allergic dysfunction, are identified as causing similar reactions to another allergic epitope. The majority of food allergens consist of four species: profilins, cupins, cereal prolamin superfamily, and homologs of *Bet v 1* (principal allergen of *Betula* pollen). The limited number of species could point to the wide cross-reactivity of IgE, even between allergens that originate from different plants (Muluk & Cingi, 2018). The phenomenon of cross-reactivity doesn't always have a clinical relevance. Surface structure sequence identity is a critical factor influencing cross-reactivity, with a threshold of 35% sequence identity commonly proposed as the minimum requirement for potential immunological cross-reactivity (Goodman *et al*, 2005). The most common cross reactivity directions are highlighted 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.	Eisheid 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

The “pollen-food allergy syndrome”, better known as the OAS (oral-allergy syndrome), represents an oral mucosa allergic sensitization caused by the consumption of raw vegetables, fruits and nuts (Ta *et al*, 2015). The most well-known symptom is irritation of the oral cavity and throat, which occurs immediately after the food touches the oral cavity and typically continues for only a short time after ingestion. The syndrome occurs in people that suffer from a pollen allergy and is triggered by the epitopes from food allergens that are very similar with epitopes from pollen allergens. The symptoms can appear after the consumption of a single aliment or can be triggered by allergens in a broad range of vegetables and fruits. For example, consuming one fruit, for example a peach, can trigger symptoms. In OAS, patients react to various foods. For example, allergy to birch pollen (inhalatory allergen that mostly manifests in spring) leads to allergic reactions at carrots or different types of fruits that have seeds. Moreover, if the patients eats peanuts, hazelnuts, or almonds, they can experience itching at the level of oral mucosa. Individuals with ragweed allergy may experience OAS when consuming banana, melon, zucchini or, cucumber (Muluk & Cingi, 2018).

The most plausible theory that associates food sensitivity and pollen allergy is the theory of shared panallergens between pollen and food allergens. Panallergens are common minor allergens that lead to cross-reactions. sIgE (specific IgE) are produced as an immune reaction to those panallergens entering the system (Caballero *et al*, 1998). In this allergy pattern, the base of sensitization is pollen.

Regarding plant-food allergens, the most studied allergen-specific protein family includes profilins, PR-10 proteins (pathogen-associated protein family), nsLTPs

(nonspecific lipid transfer proteins), 7S/11S and 2S albumins (storage proteins), and CCDs (cross-reactive carbohydrate determinants).

1.1. PR-10

The first allergen identified from this family was *Bet v 1*, allergen from *Betula verucosa* pollen. If a test for this allergen is positive in an area without or with very few trees, it often means that the patient is allergic to homologs from related tree species or grass pollens. Up to 90% of patients allergic to Birch pollen present different associated allergies to pollen and food (Menz *et al*, 1996). PR-10 proteins are very often found in the fruit pulp. The manifestations are mild and present only at the level of oral mucosa. In contrast to profilins are nonspecific lipid transfer proteins, PR-10 proteins are moderately resistant to heat and are labile to changes in pH.

1.2. Profilins

Profilins, of approximately 12-15 kDa in size, are actin-binding proteins. They can represent a key part in the regulation of intracellular transport, cell division and morphogenesis. Profilins are panallergens with a high cross-reactive rate. The species that contain profilins are implied in multiple pollen-food sensitizations, which are not relevant from a clinical point of view because the species are distantly related (Hoffmann-Sommergruber & Mills, 2009). Sensitization that implies profilins often includes symptoms appeared after consuming banana, melon, tomato and citrus. In patients with pollen allergies from Southern and Central Europe, profilins are present in a range of 10-35%, this percent being lower in Northern Europe (Asero *et al*, 2008). The rate can increase up to 55% in cases of polysensitization, especially when the allergies are caused by grass (Valenta *et al*, 1991). Even if irradiation, heat or pressure treatment is applied, the binding activity of immunoglobulins E is not negatively impacted. The clinical manifestations vary from mild to severe symptoms, oral allergy syndrome being the main expression of food allergies (Vieira *et al*, 2012).

1.3. Nonspecific lipid transfer proteins

Nonspecific lipid transfer proteins measure about 9-10 kDa and are molecules of small size. They participate in galactolipids and phospholipids transport through membranes. Being panallergens, they are present in the tissues of many plants and lead to cross-reactive reactions between fruits and vegetable, including cherries, cabbage, nuts, apples, lettuce, sweet chestnuts (Hoffmann-Sommergruber & Mills, 2009). Grapes and wine, which have also caused oral allergy syndrome in patients, probably contain

homologs and cross-reactive nsLTP with panallergens from peaches (Pastorello *et al.*, 2003). They have a high threshold of resistance to enzymatic (pepsin) and heat treatment and are stable as structure. Besides leading to oral allergy syndrome, sensitization symptoms involving nonspecific lipid transfer proteins tend to be more severe and systemic (Vieira *et al.*, 2012).

The allergic reaction to *Parietaria pollinosis*, wide spread in the mediterranean region, is rare but always associated with pistachio allergy (Liccardi *et al.*, 1996; Liccardi *et al.*, 1999). On the other hand, *Artemisia* allergy appears in multiple pollen-food syndromes from different aliment families: hot pepper, carrot, almonds, peaches, caraway, coriander, fennel seeds, celery, bell pepper, mango, garlic, leek, chamomile infusion, onion, cabbage, broccoli, parsley, peanut, mustard. However, nonspecific lipid transfer protein from *Artemisia vulgaris* pollen (*Art v 3*) can be positive on its own, without sensitization to other proteins (Gadermaier *et al.*, 2009). Also, the probability of *Par j 2* (allergen of *Parietaria judaica* pollen) being cross-reactive with other nonspecific lipid transfer proteins is low (Ciardiello *et al.*, 2010).

2. DETERMINATION OF CROSS-REACTIVE ALLERGIES

2.1. Microarray Technique

In the field of allergies, the microarray technology is a relatively novel approach. The inability to standardize the natural allergen extracts used in conventional skin testing is the reason for the need for better procedures. The molecules producing sensitization are not identified by the IgE-mediated allergy diagnostic, but the allergy source is. (Vieira *et al.*, 2012)

It is now possible to quantify specific IgEs for particular allergen components quantitatively. This component-based diagnosis provides a thorough IgE reactivity profile for each patient and is based on natural or recombinant allergens that have immunobiological and structural properties similar to those of natural sources (Valenta *et al.*, 1999). The microarray technique is used to determine sensitivity to many allergenic components (natural, refined, or recombinant allergens) from a single serum sample (Lucas, 2010). Skin tests using traditional extracts have poor allergenic potency and low specificity when diagnosing suspected food allergies (EEACI Subcommittee, 1993; Sampson, 2002). An alternative is to use fresh meals, although this has issues with repeatability (Ortolani *et al.*, 1989) and increases the risk of negative reactions, such as allergy, particularly in youngsters (Devenney *et al.*, 2000; Liccardi, 2006). However, there is no consensus on standardized processes, and these procedures are not yet fully developed (Asero *et al.*, 2007). Furthermore, only physicians with the necessary allergy

training should use these techniques, and they must all be carried out in a secure setting. The specificity of identifying particular IgE using entire extracts is the lowest of all in vitro techniques (Lucas, 2010; Sampson, 2002). By getting over the aforementioned restrictions, purified natural or recombinant allergens have shown promise (Valenta *et al*, 1999; Vieths *et al*, 2001).

When classifying particular allergen IgE, biological cross-reactivity might be a significant but not exclusive feature. The ability to perform multiple IgE measurements with single protein allergens, particularly using the microarray technique, is a helpful, straightforward, and non-invasive diagnostic component for complex polysensitized allergic patients, according to studies on microarray-based IgE detection in polysensitized allergic patients suspected of food allergy (Vieira *et al*, 2011).

2.2. ISAC Tests

The precise food ingredients that cause patient sensitivity can be identified using recombinant proteins. According to the World Allergy Organization, patients whose clinical symptoms and IgE-based testing are not conclusive can benefit from a molecular allergy diagnosis. When choosing immunotherapy, molecular allergies can be helpful. According to Canonica *et al* (2013), patients who exhibit ambiguous sensitization patterns or are polysensitized may benefit from molecular allergy testing. Furthermore, in patients who are sensitized to components with comparable epitopes, cross-reactivity is easily detected. The ImmunoCAP ISAC-Immuno-Solid phase Allergen Chip (Thermo Fisher Scientific/Phadia AB) is the multiplex platform for molecular allergy diagnosis currently used in medical practice. It consists of a biochip that contains 112 different allergens from 51 different sources (such as foods, pollen, and animals) fixed on a microarray that enables the semi-quantitative determination of specific IgE antibodies (Westwood *et al*, 2016; Hamilton *et al*, 2015; Maesa *et al*, 2021).

Given that ISAC tests are safe and accessible to allergists outside of hospital settings, they offer many benefits, including the ability to help diagnose children and patients at risk of systemic symptoms (Goikoetxea *et al*, 2010; Vieths *et al*, 2001). The procedure is easier to apply to pediatric patients because less serum is needed. Additionally, ISAC accuracy has been confirmed to correlate with routine, conventional testing and to have comparable potency in terms of allergen mass (Jahn-Schmid *et al*, 2003; Wöhrle *et al*, 2006).

3. DISCUSSIONS

The procedure of diagnosing allergies in polysensitized adult and pediatric patients should be in a continually development. One of the principal needs is the need to refine the type and cause of sensitization reaction. Another need is the need of applying effective techniques in managing the allergic 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 recognizing patients that are in a high risk category for emerging systemic reactions (Vieira *et al*, 2011).

Being an IgE-mediated allergic reaction that typically occurs in response to specific food categories, the oral allergy syndrome appears due to the cross-reactive relation between pollen allergens and structurally similar food proteins. Given that the condition is often unnoticed, there are limited studies that refer its etiology, prevalence, pathogenesis, and cure (Kelava *et al*, 2014).

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