Practicals in Pediatric Allergy

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CHAPTER 5

Cross-reactivity Concepts for a Practitioner

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INTRODUCTION

Cross-reactivity is a crucial concept in allergy diagnostics and management. In pediatric allergy, understanding cross-reactivity between allergens can significantly influence both diagnostic approaches and therapeutic decisions. Cross-reactivity occurs when the immune system recognizes and reacts to similar protein structures shared between different allergens, leading to a clinical reaction to substances that were not initially identified as allergens. This chapter will cover the basic principles of cross-reactivity, its clinical relevance, and practical considerations for the practitioner.

BASIC MECHANISMS OF CROSS-REACTIVITY

Cross-reactivity occurs when immune recognition sites, known as epitopes, are shared across different allergen sources, causing IgE antibodies to react to multiple-related proteins. This phenomenon commonly occurs between botanically and zoologically-related species and is especially relevant in the context of pediatric allergy **(Fig. 5.1)**.

Pathogenesis-related 10 Proteins

PR-10 proteins (pathogenesis-related proteins) play a critical role in plant defense mechanisms and are conserved across various plant species. In allergies, PR-10 proteins are known to be cross-reactive due to their structural homology, commonly resulting in reactions to fruits and vegetables in individuals sensitized to birch pollen. The birch pollen PR-10 protein, Bet v 1, has homologues in apples (Mal d 1), cherries (Pru av 1), and carrots (Dau c 1), often causing pollen-food syndrome. PR-10 proteins are labile, sensitive to heat and digestion, and mainly associated with oral symptoms such as itching and swelling, especially when the foods are consumed raw.

Profilins

Profilins are small, highly conserved proteins involved in cellular structure, found widely across plants, animals, and fungi. In allergology, profilins act as panallergens because they are widely distributed across plant species. Sensitization to profilins can cause cross-reactivity between pollen and foods, particularly in individuals with grass or weed pollen allergies. Profilins are typically unstable (heat- and digestion-sensitive), causing mild, localized symptoms. Bet v 2 in birch pollen, Api g 4 in celery, and Cuc m 2 in melons are well-known examples, often resulting in reactions to melons, tomatoes, and other foods.

Lipid Transfer Proteins

Lipid transfer proteins (LTPs) are highly stable proteins, resistant to heat and

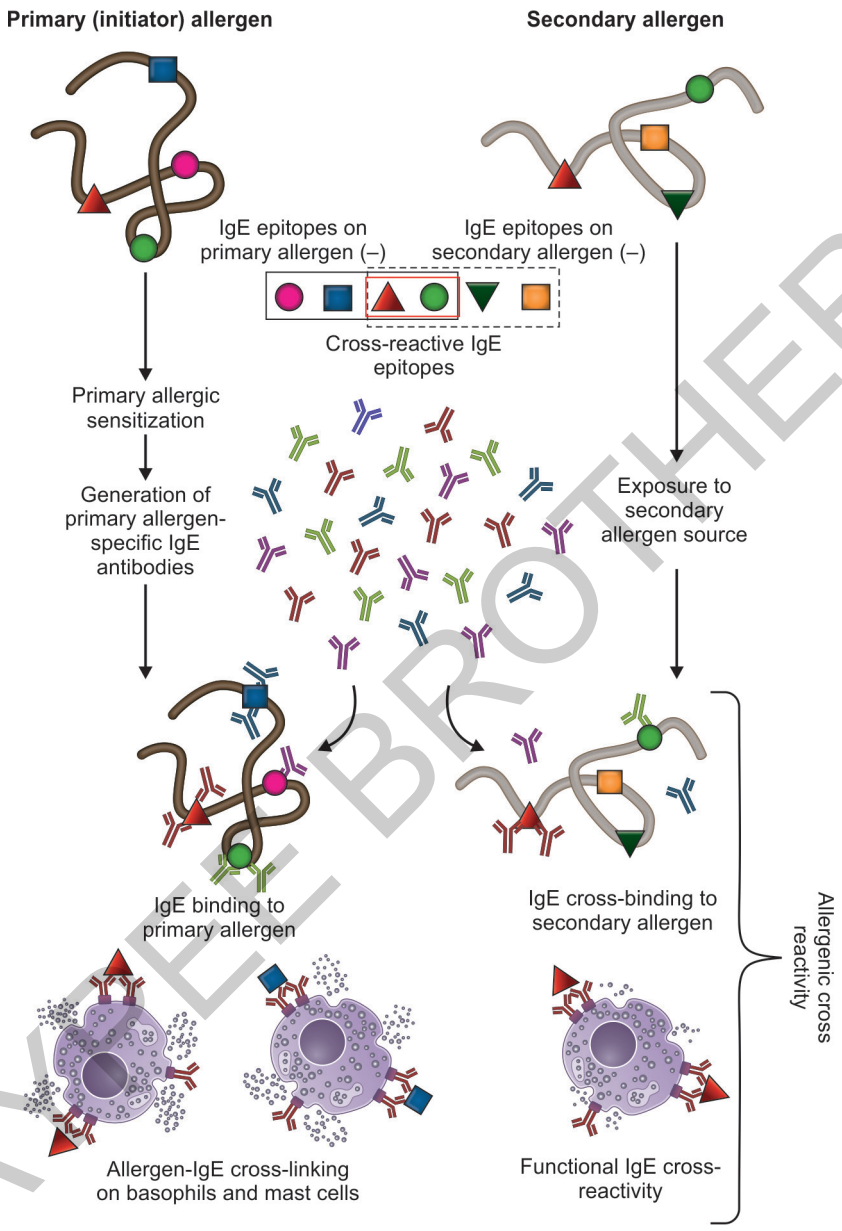

Fig. 5.1: Pathophysiology of cross-reactivity.

digestion, found in many plant foods. Their structural resilience allows LTPs to trigger systemic reactions, including anaphylaxis. This stability makes LTPs particularly significant in cross-reactivity, especially in Mediterranean populations, where severe allergic responses to fruits such as peaches and apricots are common. For example, Pru p 3, an LTP in peaches, is cross-reactive with the LTP Cup s 3 in cypress pollen, leading to

significant food-pollen cross-reactivity and an increased risk of severe reactions.

Tropomyosins

Tropomyosins are muscle proteins found in invertebrates, including crustaceans, house dust mites, and mollusks. Due to their high structural similarity, tropomyosins act as panallergens, causing cross-reactivity between dust mites, shrimp, and other shellfish. Tropomyosins are stable to heat and digestion, often causing severe allergic reactions even after cooking. For instance, Der p 10 in house dust mites and tropomyosins in shrimp highlight how cross-reactivity extends between inhalant and food allergens, making it essential for clinicians to recognize the risks associated with these stable proteins.

CLINICAL IMPLICATIONS OF CROSS-REACTIVITY

Understanding cross-reactivity's clinical implications is essential for practitioners, especially when distinguishing between sensitization and true allergy **(Table 5.1)**. Cross-reactivity may result in widespread sensitization to multiple biologically-related allergens, though not all cases lead to clinically significant reactions. The implications of cross-reactivity are influenced by factors such as the type of allergen (degree of protein homology, stability), the patient's immune response, and environmental or cofactors that can enhance the clinical severity of reactions.

Pollen-food Syndrome

Also known as oral allergy syndrome, *pollen-food syndrome* (PFS) is the most recognized form of cross-reactivity. It occurs primarily in individuals sensitized to specific pollens, leading to mild symptoms, typically localized to the oral cavity, when consuming certain raw fruits or vegetables. For example, birch pollen-allergic individuals often experience itching or swelling in the mouth when consuming foods such as apples, cherries, or carrots, which share homologous proteins (PR-10 family) with birch pollen's Bet v 1. Studies indicate that PFS affects a significant portion of the population in regions with high birch pollen exposure, with the prevalence varying between 20 and 50% in different geographic areas.

House Dust Mite and Shellfish Cross-reactivity

Tropomyosins, structural proteins highly conserved across invertebrates, are responsible for cross-reactivity between house dust mites and shellfish. Patients sensitized to dust mites may develop allergic reactions to crustaceans such as shrimp, lobster, and crabs. The stability of tropomyosins to heat and digestion often results in systemic reactions, including anaphylaxis. For example, tropomyosin Der p 10 in house dust mites and Pen m 1 in shrimp highlight the cross-reactive potential that poses a clinical challenge. Such cross-reactive reactions are more prevalent in regions with high house dust mite exposure and seafood consumption.

Latex–fruit Syndrome

This syndrome involves cross-reactivity between latex and certain fruits such as bananas, avocados, and kiwis. Latex contains proteins such as Hev b 6.02, which shares structural similarity to proteins in these fruits. This cross-reactivity is particularly relevant in clinical settings, where individuals repeatedly exposed to latex, including healthcare workers and patients with frequent medical procedures, are at a higher risk. For example,

TABLE 5.1: Common cross-reactivities.

Primary allergen	*Source*	*Cross-reactive foods/ allergens*	*Typical symptoms*	*Notes*
Birch pollen (Bet v 1)	Trees (Birch)	Apples, pears, carrots, celery, almonds, cherries	Oral itching, tingling, swelling of mouth/throat	Common in birch pollen allergy regions; related to PR-10 proteins
Grass pollen	Grasses (e.g., Timothy)	Melons (watermelon, cantaloupe), tomatoes, oranges	Oral allergy symptoms, sometimes mild GI discomfort	Patients with grass pollen allergies often react to fruits/vegetables related to profilins
House dust mite	*Dermatophagoides* species	Shrimp, lobster, crab	Systemic reactions, including potential for anaphylaxis	Tropomyosin cross-reactivity; reactions can be severe, especially in adults
Latex	Natural rubber latex	Bananas, avocados, kiwis, chestnuts, passion fruit	Oral itching, swelling, potential for systemic reactions	Latex–fruit syndrome; significant in healthcare settings due to latex exposure
Ragweed pollen	Weeds (Ragweed)	Melons (watermelon, cantaloupe), bananas, cucumbers, zucchini	Oral allergy symptoms, itchy mouth/throat	Often seen in regions with high ragweed pollen; related to profilin proteins
Mugwort pollen	Weeds (Mugwort)	Celery, carrots, spices (e.g., parsley, coriander)	Oral itching, GI symptoms, occasionally systemic symptoms	Known as the Mugwort–Celery–Spice syndrome, also related to profilins
Cypress pollen	Trees (Cypress)	Peaches, oranges, apples, kiwi	Oral itching, swelling, GI symptoms	LTP cross-reactivity, common in Mediterranean populations

Contd...

Contd...

Primary allergen	***Source***	***Cross-reactive foods/ allergens***	***Typical symptoms***	***Notes***
Cat dander	Cat fur, dander	Pork (rare cross-reactivity)	GI discomfort, potential for systemic reactions	Rare cross-reactivity known as "pork–cat syndrome"
Peanut	Legumes (Peanut)	Tree nuts (almonds, hazelnuts, cashews), soybeans	Oral itching, swelling, anaphylaxis (severe cases)	Significant in children; cross-reactivity due to similar storage proteins
Ficus	Ficus plants	Latex, bananas, avocados	Oral itching, respiratory symptoms	People with fig (Ficus) allergies may also react to latex-related foods
Ash pollen	Trees (Ash)	Olives	Oral itching, swelling, mild respiratory symptoms	Related to olive pollen cross-reactivity in Mediterranean regions
Sunflower seed	Sunflower plants	Melons (watermelon, cantaloupe), other seeds	Oral itching, mild GI symptoms	Related to seed allergies, often appears with other pollen allergies
Buckwheat	Buckwheat	Other cereals (rare cross-reactivity with rice, wheat)	GI symptoms, respiratory symptoms, occasionally severe	Not common, more likely in regions with high buckwheat consumption

(GI: gastrointestinal; LTP: lipid transfer protein; PR: pathogenesis-related)

children with spina bifida, who often undergo multiple surgeries, are especially vulnerable to latex sensitization and subsequent cross-reactive responses to certain foods.

Legume Allergy

Legumes, such as peanuts, soybeans, and chickpeas, frequently exhibit cross-reactive allergic responses due to shared proteins. Peanut allergy, a common legume allergy, is often linked with cross-reactivity to other legumes and tree nuts. This adds complexity in clinical management, as sensitization to peanuts does not necessarily mean a clinical reaction to all legumes, underscoring the need for individualized testing and dietary recommendations.

Tree Nut Allergy

Cross-reactivity is prevalent within tree nuts, including walnuts, almonds, cashews, and hazelnuts, due to shared protein structures. Management of tree nut allergies is complex since reactions to one type of tree nut can sometimes indicate cross-sensitization without a true clinical reaction to all nuts, requiring a nuanced approach to dietary restrictions.

Fish Allergy

Fish allergies are frequently related to the parvalbumin protein, which is consistent across many fish species such as salmon, tuna, and cod. This homology often results in cross-reactive responses to multiple fish types, though it does not extend to shellfish, allowing for specific dietary recommendations based on fish-only sensitization.

Hen's Egg Allergy

Commonly seen in children, hen's egg allergy is associated with proteins such as ovomucoid and ovalbumin. While some children outgrow this allergy, others remain sensitized to both raw and cooked egg proteins. Limited cross-reactivity may occur with eggs from other birds, but this is not universal, enabling targeted management strategies.

Cow's Milk Allergy

Cow's milk allergy, particularly common in infants, can present with cross-reactive sensitization to milk from other mammals, such as goat and sheep, due to similar casein and whey proteins. This allergy often manifests with gastrointestinal and respiratory symptoms, and although some children outgrow it, others require long-term avoidance of all mammalian milks.

CO-ALLERGY CONSIDERATIONS AND RELATED RISKS

Co-allergies are frequently observed among patients with multiple food or environmental sensitivities, such as peanut and tree nut allergies or sensitivities to tree pollens and certain fruits. These co-allergies complicate diagnostic processes, as overlapping symptoms may mask true allergenic sources. Component-resolved diagnostics (CRD) and oral food challenges play a critical role in differentiating primary allergens from clinically irrelevant cross-reactive sensitizations.

Diagnostic and Management Considerations

Given the prevalence and variable clinical impact of cross-reactivity, a structured approach is essential **(Table 5.2)**.

Component-resolved Diagnostics

The use of molecular allergology, or CRD, allows for precise identification of the

TABLE 5.2: Comparison of various diagnostic tools in cross reactivity.

Diagnostic tool	*Purpose*	*Sensitivity*	*Specificity*	*Use cases*
Skin prick testing (SPT)	Detect sensitization to allergens	High for inhalants	Moderate for foods	Initial allergy diagnosis, screening
Component-resolved diagnostics (CRD)	Identify specific allergenic proteins	High (component-level)	High	Differentiating primary vs. cross-reactivity
Oral food challenge (OFC)	Confirm clinical allergy	Gold standard	High	Confirmation of food allergy in cross-reactivity

specific allergen components responsible for sensitization. This diagnostic technique helps differentiate between primary sensitization to an allergen and cross-reactive responses that might not result in clinical symptoms. CRD enables the detection of IgE antibodies specific to particular allergenic proteins, such as Bet v 1 in birch pollen allergy, which can indicate a potential cross-reactivity with foods such as apples and carrots. By pinpointing the exact proteins involved, CRD reduces the likelihood of overdiagnosing allergies based on cross-reactive sensitizations, helping practitioners focus on clinically relevant allergens.

Oral Food Challenges

In situations where CRD suggests potential cross-reactivity, but the clinical significance remains uncertain, oral food challenges (OFCs) serve as the gold standard to confirm or rule out actual food allergies. During an OFC, the patient is gradually exposed to the suspected food allergen under controlled conditions to observe any allergic reactions. This method is particularly valuable for children sensitized to multiple related foods, as it minimizes unnecessary dietary restrictions by identifying only those allergens that cause significant symptoms upon ingestion.

Immunotherapy Options

Allergen immunotherapy (AIT) can be a useful intervention for managing cross-reactive allergies, especially in cases where inhalant allergens, such as pollen, also lead to food-related symptoms. For instance, immunotherapy for birch pollen has been shown to alleviate symptoms associated with cross-reactive foods in patients with PFS. However, due to the complexity of cross-protective effects, immunotherapy decisions should be carefully considered. Stable allergens, such as LTPs and tropomyosins, which can trigger severe reactions, may require cautious assessment before immunotherapy is initiated, weighing the potential benefits against risks.

SUMMARY

Cross-reactivity represents a substantial consideration in pediatric allergy, influencing diagnostic and management strategies. By understanding protein families such as PR-10, profilins, LTPs, and tropomyosins, and integrating advanced diagnostics and tailored management plans, practitioners can effectively address the challenges posed by cross-reactive allergies and enhance patient outcomes.

KEY POINTS

- Cross-reactivity occurs when IgE antibodies recognize structurally similar proteins across different allergen sources, significantly influencing pediatric allergy diagnosis and management.
- Major protein families include *PR-10 proteins, profilins, lipid transfer proteins (LTPs),* and *tropomyosins,* each differing in stability and clinical relevance.
- *Common syndromes: Pollen–food syndrome, house dust mite–shellfish cross-reactivity,* and *latex–fruit syndrome,* ranging from mild oral symptoms to systemic, potentially severe reactions.
- Cross-reactivity also complicates *legume, tree nut, fish, egg, and milk allergies,* making individualized testing and dietary planning essential.
- *Diagnostic tools:* Skin prick test (SPT) for screening, component-resolved diagnostics (CRD) for precision, and oral food challenges (OFC) as the gold standard to confirm true clinical allergy.
- *Management* focuses on accurate diagnosis, avoiding unnecessary dietary restrictions, and selective use of allergen immunotherapy, with special caution for stable allergens such as LTPs and tropomyosins.

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Practicals in Pediatric Allergy

Practicals in Pediatric Allergy is the first-of-its-kind book from India, dedicated to the practical aspects of allergy diagnosis and management in children. The chapters have been contributed by a diverse group of experts from both India and abroad, bringing together a wide range of perspectives and clinical experiences to offer a comprehensive resource for healthcare professionals.

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