Carbohydrate Determinants:

A Common Cause of False Positives in IgE Allergy Testing

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Identification of antigens responsible for food and environmental allergies is generally performed using allergen-specific IgE antibody tests. However, there are times when patients who test positive for allergen-specific IgE antibodies against a certain food or pollen show no symptoms when encountering the identified allergen. When these false positives occur, the clinician should be aware of a cross-reaction that occurs between allergen-specific IgE antibodies and cross-reactive carbohydrate determinant (CCD) antigens.[1]

CCDs are sugars that bind with proteins in a glycosylation reaction that results in the formation of glycoproteins. CCDs are commonly found in plants and pollens. For example, peanut proteins are significantly mannosylated and many pollen proteins are N-glycosylated with a well-known 6-sugar structure.[2] Peptide-specific IgE antibodies, which are the primary agents involved in allergic manifestations, may mistakenly recognize glycoepitopes, leading to false positive results.[2]

The CCD component of glycosylated proteins derived from plants and invertebrates are distinct from glycoproteins found in humans and therefore are immunogenic. Despite their immunogenicity, in most cases, CCDs do not produce a hypersensitivity reaction, likely because no cross-linkages are formed between the CCD and the anti-CCD-specific IgE antibodies on the mast cell membrane, inhibiting degranulation and resulting little if any histamine release.[3]

More Than One Type of CCD

However, there are two types of CCDs. The first is galactose-alpha-1,3-galactose (α-gal). This type of CCD may have clinical relevance as it is the agent associated with the delayed anaphylactic reaction to meat that develops in many individuals bitten by the lone star tick.[4] It was also responsible for the anaphylactic reactions of patients that were given the colon-cancer drug cetuximab.[4] The second form of CCD has a sugar structure known as MUX, containing mannose, glucose, and xylose. This type of CCD is often clinically unimportant. However, it may lead to false-positive results because it cross-reacts with antigens from foods or pollens.[5]

It is estimated that 22% to 23% of allergic individuals are sensitized to plant/insect CCDs.[5,6] The prevalence is greater in teenagers (35%) and in subsets of patients with multiple pollen sensitization (71%), and with a previous pollen immunotherapy course (46%).[5,6]

A Different Type of Cross-Reactivity

There are many cross-reactivities that occur between pollens and food allergens as well as cross-reactivity between food groups. For example, individuals who are allergic to birch pollen can also become allergic to celery and carrot and cow's milk allergy can cross-react with veal.[7] For a comprehensive list of these cross-reactive syndromes, see the table in this article.

Cross-reactivity occurs when IgE antibodies in the body are able to recognize similar (homologous) allergens from different species that share the same epitopes. Many of these cross-reactions are clinically important with the patient experiencing symptoms after eating the cross-reactive food. However, with CCDs, as noted above, in most cases there are no reactive symptoms after exposure to the CCD allergen. The false positives caused by CCDs have been found to occur with a large number of foods and pollens. Sensitization to CCDs caused by pollen from timothy grass and mugwort or wasp/bee venom allergens, can lead to false-positive IgE antibodies against natural rubber latex and apples.[8]

The human immune system can recognize CCDs, leading to the production of

antibodies to cross-reactive carbohydrate determinants (anti-CCDs). For example, these anti-CCDs have been found in sera from grape-sensitive individuals.[2] Researchers investigated poly-allergic subjects who had oral allergy syndrome after eating fresh grapes but had a negative skin prick test with grape extract.[2] Sera from those same subjects reacted strongly in ELISA and Western blotting testing using grape extract. These discrepancies are thought to be due to anti-CCDs. The researcher concluded that anti-CCD antibodies "may cause weakly false-positive results during assessment of IgE reactivity to grape allergens." The presence of anti-CCD IgE antibodies in allergic patients' sera may result in significant in vitro immunoreactivity with glycoepitopes, contributing to differences between in vivo and in vitro assays.[9]

The presence of CCD-related antigen-specific IgE antibodies can vary based on the type of allergy. A study of patients who had pollen-specific IgE antibodies detected a higher presence of CCD-related antigen-specific IgE antibodies in participants with ragweed pollen allergy compared with those who had orchard grass and Japanese cedar pollen allergies.[1] There was also slight cross-reactivity between anti-CCD, Japanese cypress, and orchard grass. According to the study authors, "These results, from the viewpoint of antigenicity, suggest that epitopes are shared between ragweed pollen- and CCD-related allergen-specific IgE antibodies. These results also indicate that specific IgE antibodies to ragweed pollen and CCD-related allergens antibodies are more likely to cross-react." The researchers proposed an intriguing potential method for treating pollen allergy sufferers. Specifically, they suggest that during the pollen season, administering CCD-related antigens to people with pollen allergies may block the type 1 hypersensitivity reaction through the binding of IgE antibodies in those individuals with CCD-related antigens instead of the pollen allergens.[1]

In addition to investigating CCDs in pollen allergies, these same researchers measured titers of CCD-specific IgE antibodies in 12 individuals who tested positive for soybean-specific IgE antibodies and five patients who were positive for wheat-specific IgE antibodies.[1] All of the subjects tested positive for CCD-specific IgE antibodies. Because these patients showed no subjective symptoms from soybean or wheat allergies, the results likely indicated false positives due to the cross-reactivity between CCD-related antigen-specific IgE antibodies and soybean and/or wheat allergens.

Glycoproteins from bromelain and horseradish peroxidase share similar specific IgE binding structures to plant CCDs against which specific IgE antibodies can be generated.[5] However, unlike allergens, these glycoproteins are less likely to produce a type I hypersensitivity reaction and related symptoms. Consequently, sensitization to CCD is often determined via positive IgE testing for bromelain or horseradish peroxidase glycoproteins.[8]

Conclusion

Cross-reactive carbohydrate determinants are an important consideration when testing patients for allergies. In patients who test positive for an IgE reaction to foods or pollen but yet exhibit no symptoms, allergic mimicry due to cross-reaction between allergen-specific IgE antibodies and CCDs should be suspected.

Select Potential False-Positive IgE Reactions Due to CCDs

- Grapes
- Ragweed
- Soy
- Wheat
- Japanese Cypress
- Orchard Grass
- Natural Rubber Latex
- Apples
- Hymenoptera (Bees, wasps, etc.) Venoms

Common Cross-Reactions Between Food, Pollen, Fungi, and Animal Allergens[7,10,11,12]				
Food or Other Allergen	**Pollen Allergies**			**Other Allergies**
	Trees	**Grasses**	**Weeds**	**Other Allergens**
Apple	Alder, Birch	Cocksfoot, Timothy Grass	Mugwort	Latex
Hazelnut	Alder, Birch, Plane Tree		Mugwort	Latex
Celery	Alder, Birch, Plane Tree	Grass spp.	Mugwort	Latex
Carrot	Alder, Birch		Mugwort	Latex
Peach	Alder, Birch, Cypress, Olive Tree	Grass spp.	Mugwort	Latex
Pear	Alder, Birch, Olive Tree		Mugwort	Latex
Kiwi	Alder, Birch, Olive Tree, Ornamental Ficus	Grass spp.	Mugwort	Latex
Banana	Olive Tree, Plane Tree		Ragweed	Latex
Fig	Ornamental Ficus			Latex
Pineapple	Ornamental Ficus			Latex
Avocado	Ornamental Ficus			Latex
Papaya	Ornamental Ficus			Latex
Cantaloupe	Olive Tree	Bermuda Grass	Mugwort, Ragweed	Latex
Tomato		Bermuda Grass	Ragweed	Latex, Tobacco
Paprika			Mugwort	Tobacco
Pepper	Birch		Mugwort	Latex, Tobacco
Almond	Alder, Birch		Mugwort	Latex
Honeydew Melon	Olive Tree	Grass spp.	Mugwort, Ragweed	Latex
Crustacea and Mollusks				Cockroach, Dust Mites, other Crustacea/Mollusks
Pork				Beef, Cow's milk, Cat and Dog Dander,
Eggs				Duck, Goose, and Turkey eggs, Avian dander, feathers, and meat
Cow's Milk				Beef, Buffalo, Goat, Lamb

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Food or Other Allergen	**Pollen Allergies**			**Fungal Allergies**
	Trees	**Grasses**	**Weeds**	**Molds and Yeasts**
Leek			Mugwort	
White Mustard			Mugwort	
Indian Mustard			Mugwort	
Cabbage			Mugwort	
Broccoli			Mugwort	
Cauliflower			Mugwort	
Zucchini	Birch		Mugwort, Ragweed	
Cucumber			Ragweed	
Echinacea			Ragweed	
Pistachio			Mugwort, Parietaria	
Spinach				*Alternaria alternata*
Agaricus bisporus				*Alternaria alternata*
Wheat		Timothy Grass		
Orange	Alder, Birch, Japanese Cedar	Orchard Grass, Timothy Grass		
Parsley	Alder, Birch		Mugwort	
Caraway			Mugwort	
Fennel	Alder, Birch	Grass spp.	Mugwort	
Coriander Seeds	Birch		Mugwort	
Aniseed	Birch		Mugwort	
Garlic			Mugwort	
Onion			Mugwort	
Soy	Birch			
Watermelon	Olive Tree	Grass spp.	Mugwort, Ragweed	
Latex	Olive Tree	Grass spp.	Mugwort, Ragweed	
Peanut	Plane Tree	Grass spp.	Mugwort	

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