Cross-Reactive Aeroallergens: Which Need to Cross Our Mind in Food Allergy Diagnosis?

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Learning objectives:

1. To evaluate patients with possible food allergy based upon aero-allergen cross-reactive food proteins.

2. To describe proteins responsible for food-aeroallergen cross reactivity.

3. To recognize the potential severity of aeroallergen-food allergen cross-reactivity.

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Secondary food allergies due to cross-reactivity between inhalant and food allergens are a significant and increasing global health issue. Cross-reactive food allergies predominantly involve plant-derived foods resulting from a prior sensitization to cross-reactive components present in pollen (grass, tree, weeds) and natural rubber latex. Also, primary sensitization to allergens present in fungi, insects, and both nonmammalian and mammalian meat might induce cross-reactive food allergic syndromes. Correct diagnosis of these associated food allergies is not always straightforward and can pose a difficult challenge. As a matter of fact, cross-reactive allergens might hamper food allergy diagnosis, as they can cause clinically irrelevant positive tests to cross-reacting foods that are safely consumed. This review summarizes the most relevant cross-reactivity syndromes between inhalant and food allergens. Particular focus is paid to the potential and limitations of confirmatory testing such as skin testing, specific IgE assays, molecular diagnosis, and basophil activation test. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1813-23)

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Respiratory allergies are a significant and increasing global health issue that affects children as well as adults.[1-3] Over the last decades it has emerged that in many patients the clinical phenotype of an inhalant allergy extends beyond their respiratory symptoms (eg, rhinoconjunctivitis and bronchospasms) and also comprises heterogeneous symptoms on food consumption

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Abbreviations used

BAT- Basophil activation tests
CCD- Cross-reactive carbohydrate determinant
CRD- Component resolved diagnosis
GRP- Gibberellin-regulated protein
HDM- House dust mite
NRL- Natural rubber latex
ns-LTP- Nonspecific lipid transfer protein
OAS- Oral allergy syndrome
PFS- Pollen-related food syndrome
PR-proteins- Pathogenesis-related proteins
sIgE- specific IgE
SPT- Skin prick test
TLP- Thaumatin-like protein

adding to a significant reduced quality of life, morbidity, and eventually also mortality.[4-7] These food allergic symptoms result from a cross-reactivity between inhalant and food allergens due to the production of cross-reactive specific IgE (sIgE) antibodies that are directed against structural homologous allergens from a taxonomically more or less related allergenic source. In these so-called secondary food allergies, allergic symptoms might vary from localized reactions restricted to the oropharynx to severe generalized and potentially life-threatening reactions. However, cross-reactive sIgE antibodies do not necessarily cause clinical symptoms and can go completely asymptomatic. The best known example of such a cross-reactivity syndrome is the pollen-related food syndrome (PFS), formerly called the "oral allergy syndrome (OAS)" as in most patients food-induced symptoms are confined to the oral cavity. However, the term OAS is misleading, as cross-reactive allergic symptoms on plant food are not necessarily limited to the oral cavity and, vice versa, allergic symptoms restricted to the oropharynx might also occur in patients without pollinosis. Therefore, in this review article, for clarity we decided to avoid the term OAS and we will literally describe symptoms involved in the PFS.

Severity of clinical symptoms is believed to mainly depend on the physical properties of the sensitizing component. In (older) children, adolescents, and adults, secondary food allergies predominantly involve plant-derived foods resulting from a prior sensitization to cross-reactive components present in pollen, latex, other plant-derived foods, and *Cannabis sativa*.[6-9] Other cross-reactivity syndromes rest on a primary sensitization to allergens present in fungi, insects, and both nonmammalian and mammalian meat.[10-12]

Unfortunately, unlike diagnosis of inhalant allergy that can generally easily be documented applying skin and sIgE tests, correct diagnosis of these associated food allergies is not always straightforward. Actually, cross-reactivity can have a significant deleterious effect on the outcome of diagnostics, as many subjects with an inhalant allergy produce cross-reactive sIgE antibodies to food allergens without any clinical significance, in other words demonstrating no allergic symptoms on exposure. Therefore, a positive skin prick test (SPT) or sIgE result should always be interpreted extremely cautiously as it might merely reflect (cross) sensitization rather than a genuine clinically relevant allergy.[13,14] To discriminate between genuine allergy and sensitization, it has been shown that to some extent component resolved diagnosis (CRD) and/or basophil activation tests (BAT) can be helpful. In contrast to conventional sIgE antibody assays, CRD does not rely on crude extract preparations obtained from native allergens (generally poorly defined mixtures containing both allergenic and nonallergenic components) but on sIgE antibodies directed towards single components purified from natural sources or produced by recombinant techniques.[15] Therefore, this technique makes it possible to establish personalized sensitization profiles and recognize cross-reactivity patterns. The principles and applications of BAT are beyond the scope of this review but are detailed elsewhere.[16,17] It appears that this technique that awaits entrance in mainstream clinical practice, to some extent, also allows us to discriminate between clinically relevant and irrelevant sIgE results and more closely mirrors the clinical situation than simple sIgE binding assays.[18-20]

This review summarizes the most relevant cross-reactivity syndromes between inhalant and food allergens with a particular focus on potential and limitations of confirmatory testing such as skin testing, sIgE assays, and molecular diagnosis (CRD).

CROSS-REACTIVE AEROALLERGENS OF PLANT ORIGIN

As summarized in Figure 1, the majority of allergen components involved in cross-reactivity between aeroallergens and plant food belong to the group of pathogenesis-related proteins (PR-proteins), structural proteins (eg, profilins and oleosins), or seed storage proteins.[21]

Grasses

Grass pollen is currently regarded as the main cause of pollen allergy worldwide with sensitization rates varying between 10% and 30%.[22,23] Exposure to grass pollen is dependent on geographical location, and therefore it is plausible that the prevalence and clinical characteristics of food allergies due to grass pollen sensitization also exhibit geographical variations. In general, studies focusing on cross-reactive food allergies linked to 1 specific inhalant allergen are scarce, most probably because the majority of our pollen allergic patients are sensitized to multiple aeroallergens. Hitherto, most data with a specific focus on food allergies linked to grass pollen are coming from northern Europe.[4,24] Out of these studies, in which patients with a monosensitization to grass pollen were included, it appears that only 4% of patients develop a grass-pollen—related PFS.[4] However, more studies in different geographical areas are needed to obtain better insights into the prevalence and clinical features of secondary food allergies linked to grass pollen.

The other way around, grass pollen sensitization can profoundly hamper correct diagnosis of food allergy diagnosis because pollen contain various IgE-binding components or epitopes, such as profilins and cross-reactive carbohydrate determinants (CCDs), which most frequently fail to trigger effector cell degranulation *in vivo*.[13,25,26] The influence of grass pollen sensitization on food allergy diagnosis is nicely demonstrated in the study of Venter et al.[27] In this study, respectively up to 78% and 40.5% of the patients with a grass pollen allergy demonstrated a positive SPT and sIgE to wheat, whereas only 0.48% of the patients had a genuine IgE-mediated wheat allergy as proved by the challenge test. Similarly, in a study of Martens et al,[28] it was estimated that in the general population, because of grass pollen sensitization, 9% and 4.7% of the people would

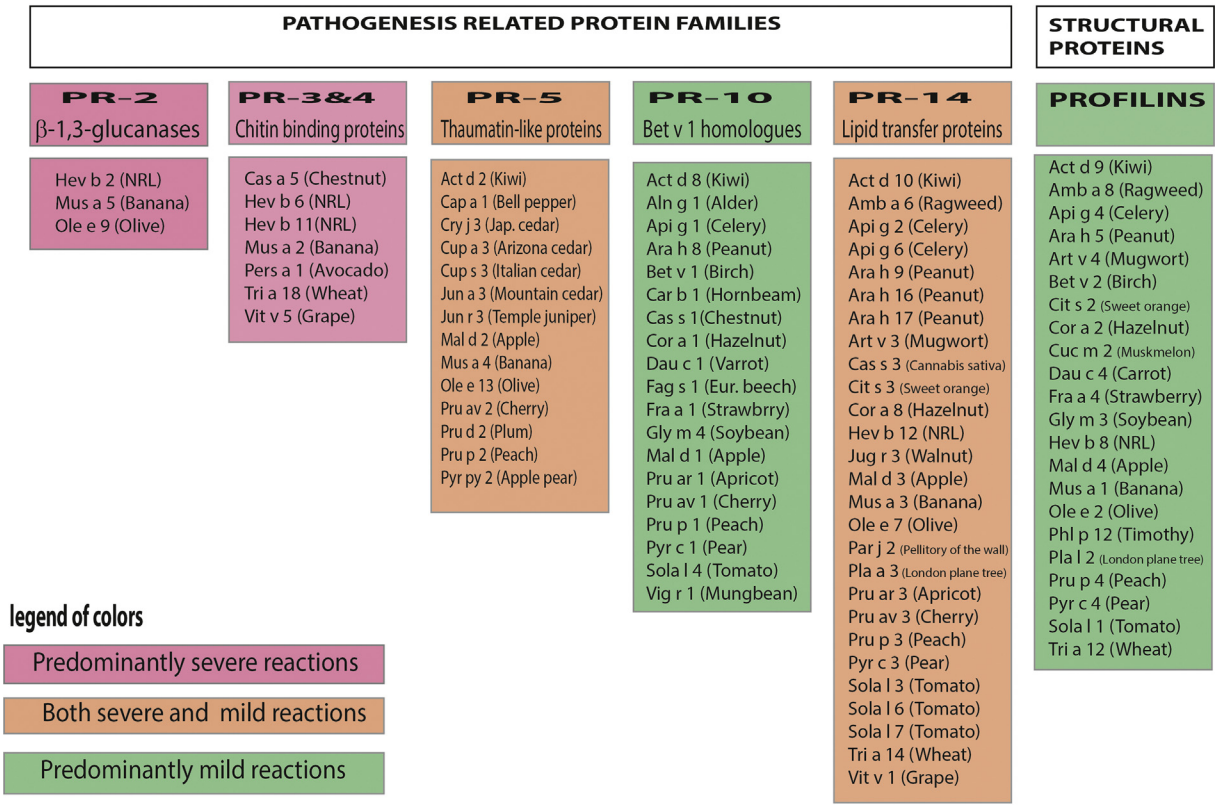

FIGURE 1. Overview of pathogenesis-related (PR) proteins and structural proteins (profilins) involved in cross-reactivity between aero-allergens and food (not exhaustive). *NRL*, Natural rubber latex.

have been erroneously diagnosed as allergic to cereals if diagnosis was only based on SPT and sIgE results, respectively.

As described above, sensitization to (grass) pollen profilins is a source for plant-derived cross-reactive food allergies only in a minority of patients.[29,30] Profilin is a structural protein present in all eukaryotic cells and does not resist thermal processing and pepsin digestion; therefore, sensitization is in general associated with symptoms restricted to the oropharynx, but severe allergic reactions to this structural protein have been rarely reported.[29,31-34] Theoretically, profilin can induce allergic symptoms to every plant-derived food, but as displayed in Figure 2, reactions predominantly involve melon, watermelon, tomato, banana, pineapple, and orange.[35] In children, kiwi, apricot, and cucumber seem also to be involved in profilin-related allergies.[36] A biomarker for profilin is Phl p 12 from timothy grass (*Phleum pratensis*).[37]

Trees

Birch. The best-known representative of the pollen-related food allergies is the "birch-fruit-vegetable syndrome" that results from a cross-reaction between the major allergen Bet v 1 from birch pollen (*Betula verrucosa*) and its labile homologues in many fruits, vegetables, and nuts. Sensitization to Bet v 1 is commonly described in the temperate climate zone of the northern hemisphere. Up to 70% of patients with birch pollen allergy can experience a "birch-fruit-vegetable syndrome"[38] mainly for Rosacea fruit (eg, apple, cherry, peach, pear), nuts (eg, hazelnut), and vegetables belonging to the *Apiacea* family (eg, celery, carrot).[4,38] Noticeably, some patients experience food allergic symptoms after typical Bet v 1 homologue—containing plant foods without suffering from inhalant symptoms during the tree pollen season. As shown in Figure 1, Bet v 1 belongs to the group of PR-proteins (PR-10). The PR-proteins are proteins that are induced in response to infections by pathogens such as fungi, bacteria, or viruses, or by noxious environmental factors.[39] The Bet v 1 homologues in plant foods are present in the peel and pulp and poorly resist both heating and gastric digestion.[40] These physiologic characteristics clarify why patients with the "birch-fruit-vegetable syndrome" generally experience localized symptoms restricted to the oropharynx when eating raw fruits, vegetables, and nuts. However, more generalized reactions are not excluded, particularly to Gly m 4 from soy (*Glycine max*).[41,42] Hitherto, the exact mechanism(s) for generalized reactions against labile Bet v 1 homologues are poorly understood, but it has been hypothesized that impairment of gastric digestion (eg, due to proton-pump inhibitors or bariatric surgery) might represent risk factors for more generalized allergic reactions in patients with a Bet v 1-related food allergy.[43-45] Like sensitization to profilins, sensitization to Bet v 1 does not necessarily trigger a birch-related food allergy and can also profoundly affect the outcome of traditional tests.[14,46,47]

Bet v 2, the birch pollen profilin, is another component able to induce cross-reactive sIgE antibodies. As exemplified in the grass pollen paragraph, the clinical relevance of sensitization to Bet v 2 is unpredictable.

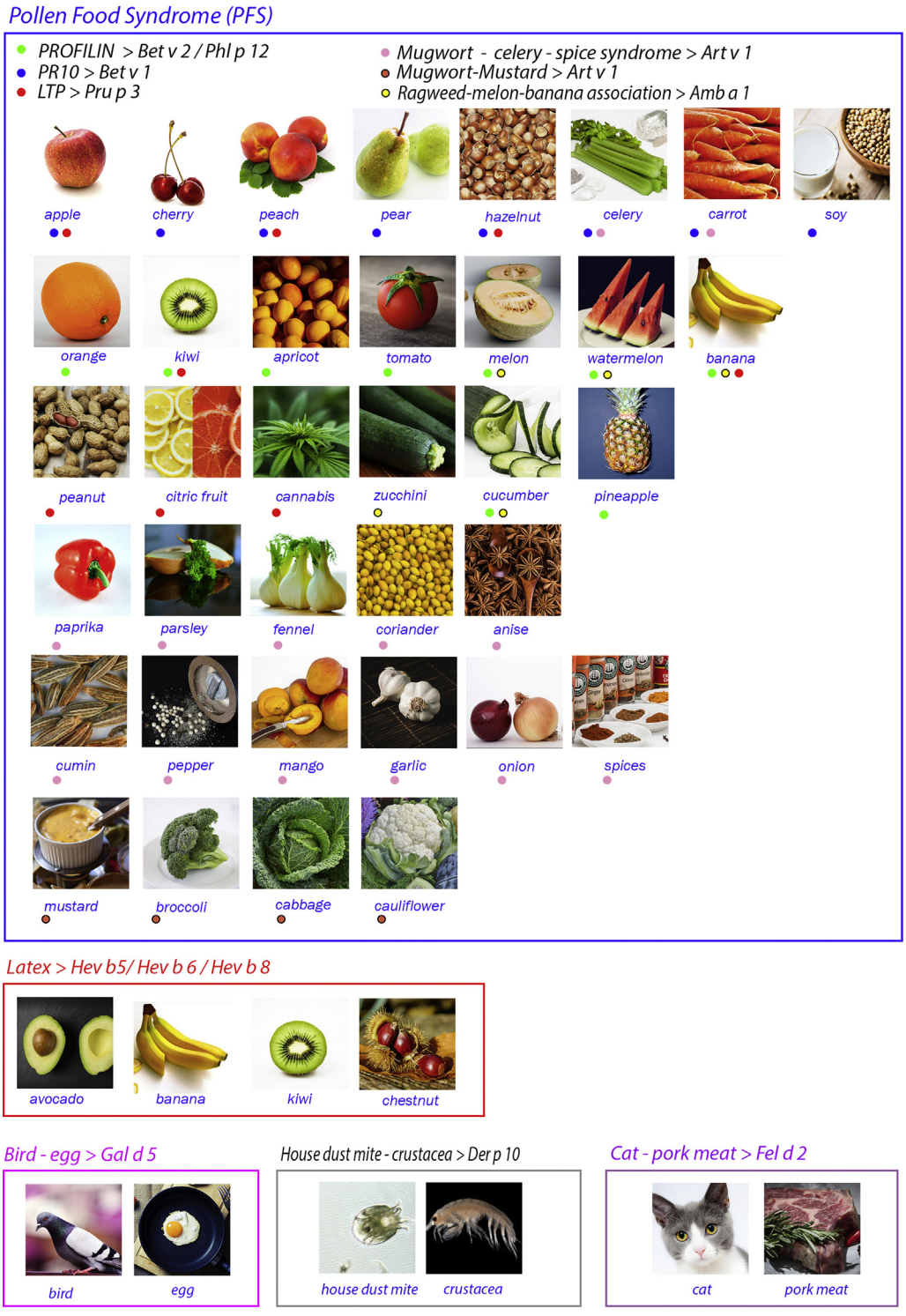

FIGURE 2. Overview of different cross-reactivity syndromes and their biomarkers (screening allergens). Colored dots in the figure display the plant foods (not exhaustive) most frequently involved in cross-reactivity between profilins (green), pathogenesis-related 10 proteins (PR-10) (blue), nonspecific lipid transfer proteins (ns-LTPs) (red), and plant foods most frequently involved in the celery-mugwort-spice syndrome (pink), mugwort-mustard allergy syndrome (orange), and ragweed-melon-banana association (white).

IgE antibodies specific for the minor allergen Bet v 6, an isoflavonoid reductase—homologous protein, have been shown to cross-react with proteins of comparable size in apple, pear, peach, orange, lychee fruit, strawberry, persimmon, zucchini, and carrot.[48]

Homologues of Bet v 7 and Bet v 8, a cyclophilin and a glutathione-S-transferase, respectively, are described in various plant foods, although cross-reactivity and clinical importance seem to be limited.[49,50]

Olive tree. Olive (*Olea europaea*) pollen are important aeroallergens, mainly in the Mediterranean area and California. Ole e 1 is repeatedly described as the major allergen in patients with olive pollinosis,[51-53] but is also recognized as a confounder in allergy diagnosis as it is highly glycosylated.[54]

Clinically relevant cross-reactions in patients sensitized to olive pollen have been described on several plant foods.[51,55] In a study of Florido Lopez et al,[55] approximately 30% of olive allergic patients experienced food allergic reactions. Peach, pear, melon, kiwi, and nuts have been reported as the predominant elicitors of secondary food allergies in patients with preexistent olive pollinosis. In a later study, the olive allergens Ole e 2, a profilin, and Ole e 7, a nonspecific lipid transfer protein (ns-LTP), are considered to be involved in the cross-reactivity with plant foods, and severity of the olive pollen—related food allergies seems to be dependent on the allergen involved in the cross-reactivity.[51] In this Spanish study, sensitization to olive profilin was detected in 90% of the patients experiencing symptoms restricted to the oropharynx, whereas severe allergic reactions were significantly associated with sensitization to Ole e 7 (ns-LTP).

Ns-LTPs belong to the PR-14 group and are recognized as important food allergens, especially in the Mediterranean basin.[56,57] Historically, sensitization towards ns-LTPs has mainly been associated with severe allergic reactions and attributed to a primary sensitization to Pru p 3, the ns-LTP from peach (*Prunus persica*).[58] However, paradigms about the ns-LTP syndrome are shifting as it appears that the ns-LPT syndrome is not necessarily governed by peach but might also be triggered by pollen.[59,60] Furthermore, patients do not necessarily exhibit severe reactions[20] but can be asymptomatic or only present a mild phenotype,[20,61] and finally the ns-LTP syndrome is certainly not restricted to the Mediterranean basin.[20,62]

Cross-reactivity between olive pollen and *Hevea* latex is also reported, and the glucanase in olive pollen (Ole e 9) might theoretically play a role in this "latex-fruit syndrome" as it demonstrates structural homology with the glucanase from natural rubber (*Hevea brasiliensis*, Hev b 2). Finally, recently a patient with olive pollinosis was reported, who developed olive fruit allergy, without having allergic symptoms to fruits other than olive, the name of "olive-olive syndrome" was proposed.[63]

Cypress. Pollen from cypresses (*Cupressus sp.pl*) are relevant inhalant allergens in the winter period, mainly for southern Europe, the coastal Mediterranean area, and Japan.[64]

The "cypress/peach syndrome" has received most attention, with symptoms ranging from mild to generalized allergic symptoms. The exact cross-reactive allergen has not yet been unraveled, although up to now 3 allergens have been proposed to be involved in the "cypress/peach syndrome."[65]

First, it has been repeatedly described that the ns-LTP of cypress pollen does cross-react with Pru p 3, the ns-LTP of peach,[60,65] and therefore could theoretically act as a trigger for the ns-LTP syndrome, although this has not yet been proven. Secondly, proteins belonging to the Snakin/gibberellin-regulated protein (GRP) family are thought to be causative allergens of the "cypress/peach syndrome."[64,66,67] Proteins of the Snakin/GRP family are widely distributed among plant species. Besides peach (Peamaclein, Pru p 7), they are also found in citrus, apples, oranges, grapes, castor beans, potatoes, and soybeans although detailed information about their allergenicity in these plant foods is still scarce.[68,69]

Finally, another allergen present in cypress pollen that might cross-react with plant foods, is Cup a 3 (*Cupressus arazonica*) belonging to the family of thaumatin-like proteins (TLPs). TLPs are identified in the pollen of cypress, birch, mugwort, olive, and plane trees.[70,71] Cross-reactivity between TLPs has been evaluated in a limited number of studies,[70,72] and only 1 study included TLPs from pollen.[70] This study of Palacin et al[70] included patients from different Spanish regions and showed evidence for cross-reactive allergy between TLPs from pollen and plant food. Because of the limited available clinical data, larger studies in different geographical areas are mandatory to evaluate the cross-reactive properties of TLPs.

Plane tree. Plane trees (*Platanus acerifolia*) are important inhalant allergens worldwide, mostly in urban regions.[73] In patients with plane tree pollinosis, hazelnuts, fruits (peach, apple, melon, and kiwi), peanuts, maize, chickpea, lettuce, and green beans are described as the most frequent causes of food allergic reactions.[74] These cross-reactive reactions cannot be explained by sensitization to the major inhalant allergens Pla 1 (invertase inhibitor) and Pla a 2 (polygalacturonase) nor by sensitization to profilins (Pla a 8).[75] Actually, the ns-LTP (Pla a 3) is assumed to be the most important allergen causing cross-reactivity to plant-derived food in plane tree allergic patients.[76,77] In a study of Scala et al,[78] a significant association was demonstrated between sensitization to Pla a 3 and having both mild symptoms restricted to the oropharynx and systemic reactions on plant food, and sensitization to Pla a 3 was inversely related to the presence of rhinoconjunctivitis or bronchial asthma.

Ficus tree. Sensitization to weeping fig (*Ficus benjamina*), a common indoor ornamental plant, can cause respiratory allergies in atopic as in otherwise nonatopic individuals.[79,80] It has been demonstrated that allergens are mainly present in the milky fluid ("latex") of the plant, and once transported to the leaf surfaces, they can accumulate in house dust, which explains the airborne sensitization route. Next to respiratory symptoms, cross-reactive allergic reactions on fresh and dried fig and other tropical fruits (eg, kiwi fruit, papaya, avocado, pineapple, and banana) are described in the so-called ficus-fruit syndrome. Figs are also involved in the "latex-fruit syndrome" as described later, but cross-reactivity in the "ficus-fruit syndrome" seems to be independent from sensitization to natural rubber latex (NRL).[79,81] Thiol proteases are assumed to be important cross-reactive allergens in this syndrome, as many patients with fig fruit allergy do show sIgE against papain, a thiol protease from papaya.[79,81,82]

Latex. NRL is obtained from the *H. brasiliensis* tree and has gained a lot of attention as allergen since the 1980s. A so-called latex-fruit syndrome has been described in 21% to 58% of individuals with an NRL allergy.[83,84] Clinical symptoms might be life threatening, and plant foods typically involved in the syndrome are avocado, banana, kiwifruit, and chestnut.[85] Among the NRL allergens, it has been demonstrated that class 1 chitinases (Hev b 6) do play a major role in the "latex-fruit syndrome." Class 1 chitinases have a defensive function, and Hev b 6 does show high sequence homology with chitinases present in fruits such as banana, avocado, and chestnut. Next to Hev b 6, many other NRL allergens (eg, profilin, glucanases, ns-LTPs) can add to the "latex-fruit syndrome." Furthermore, recently cassava (*Manihot esculenta*) and curry spice have been reported to cross-react with latex foods, and these reactions are thought to be due

to sensitization to Hev b 5 (protein with an unknown function) and Hev b 8 (profilin), respectively.[86-88] In a study of Beezhold et al,[83] cross-reactive reactions on potato and tomato were reported in NRL allergic patients; later these reactions were assigned to sensitization to Hev b 7, a patatin-like protein.[89-91] Also cross-reactive allergic symptoms on bell pepper have been described, which are thought to be due to cross-reactivity between Hev b 2, a beta-1,3-glucanase, and the bell pepper l-ascorbate peroxidase.[92] Finally, the ns-LTP of NRL (Hev b 12) has also been shown to be clinically relevant in a small number of NRL allergic patients.[93,94]

Like for other aeroallergens, sensitization to profilin (Hev b 8) might be clinically irrelevant and hamper diagnosis of NRL-related allergies, although some evidence for Hev b 8 sensitization with clinical relevancy does exist.[95-97] Finally, case reports mainly coming from France report cross-reactivity between NRL and spinach, although little is known about the eliciting allergen.[98,99]

Weeds

Mugwort. Mugwort (*Artemisia vulgaris*) is the most important allergenic weed in temperate and humid zones, and sensitization gives rise to late summer pollinosis.[100] Historically, several cross-reactive syndromes involving mugwort pollen have been described,[101-104] but on molecular level, these syndromes do not seem to rely on individual mugwort allergens but mainly ground on sensitization to panallergens such as profilins, Bet v 1 homologues, and ns-LTPs.[105]

One of the first syndromes described was the "celery-mugwort-spice syndrome," attributed to the cross-reactivity between mugwort pollen and members of the *Apiacea* family (celery, carrot, parsley, caraway seeds, fennel seeds, coriander seeds, and aniseeds).[101] But it appeared that also other botanical families such as the *Solanaceae* family (paprika), *Piperaceae* (pepper), *Anacardiaceae* family (mango), and the *Liliaceae* family (garlic, onion, leek) were involved in this cross-reactivity syndrome.[101,106,107] Currently, to the best of our knowledge, no epidemiologic data are available on the proportion of patients with an isolated mugwort allergy experiencing a mugwort-related PFS. It seems that this syndrome is caused by a mix of allergenic proteins, with a major role for profilins (Art v 4).[108,109] It has been assumed that also Bet v 1 homologues, which are not present in mugwort, play a role in this cross-reactive syndrome, and therefore it was proposed to extend the name to "celery-birch-mugwort-spice syndrome."[110] Next to profilins and Bet v 1 homologues, also high-molecular-weight allergens are described as relevant allergens in the "celery-birch-mugwort-spice syndrome" (eg, Api g 5 in celery).[111]

Another cross-reactive association with mugwort pollen is the "mugwort-mustard allergy syndrome," which most frequently presents as mild OAS on ingestion of mustard.[112] Within this syndrome, also vegetables from the Brassicaceae family (eg, broccoli, cabbage, and cauliflower) might cause allergic symptoms. Exact numbers on the prevalence of mustard allergy and/or allergic reactions on vegetable of the Brassicaceae family are lacking. However, it has been demonstrated that 37 of 38 patients with mustard allergy were sensitized to mugwort pollen and that all of these patients were allergic to other foods belonging to the Brassicaceae family.[112] The causative allergens are still a matter of intense research, but profilins, ns-LTPs, and high-molecular-weight allergens are assumed as candidates.[105,112]

Finally, also a mugwort-peach association has been proposed with the description of cross-reactivity between mugwort pollen, peach, and related Rosacea fruits. These cross-reactivities have been attributed to sensitization to ns-LTPs.[104,113,114]

Ragweed. *Ambrosia artemisiifolia* (ragweed) is a major inhalant allergen in the United States, but sensitization to ragweed is also increasing in Europe, Australia, and Asia.[115] Cross-reactivity between ragweed pollen and food was described for the first time almost 50 years ago.[116] At that time, it was given the name of "ragweed-melon-banana association," involving members of the gourd family (melon, watermelon, zucchini, and cucumber) and banana.[108,116] It has been thought that this "ragweed-melon-banana association" is mainly due to sensitization to profilin, but involvement of ns-LTPs and glycoallergens cannot be completely ruled out.[105,108]

CROSS-REACTIVE AEROALLERGENS OF FUNGAL ORIGIN

Sensitization rates for fungal species depend on geographic location and range from 6% to 24% in the general population.[117] Herrera et al[118] described the association between airborne mold allergy in asthmatics and allergic reactions to spinach and mushroom.[12,118] This phenomenon is supposed to be rare and is also referred to as "Alternaria-spinach syndrome." It has been thought to be based on cross-reactivity between a protein present in spinach and mushroom, with a molecular weight similar to the major allergens of *Alternaria alternata* (Alt a 1) and *Cladosporium herbarum* (Cla h 1).[12] Furthermore, a few case reports have been published describing patients with sensitization to inhalant fungal allergen(s), having severe IgE-mediated allergic reactions on food containing molds or yeasts.[119,120] Finally, patients sensitized to airborne mold allergens might rarely experience immediate allergic reactions on ingesting Quorn, which contains mycoprotein originating from the mold *Fusarium venenatum*.[121] It has been hypothesized that a 60S acidic ribosomal protein P2 present in *F. venenatum* is the responsible allergen for this mold-Quorn association.[122]

CROSS-REACTIVE AEROALLERGENS OF INVERTEBRATE ANIMAL ORIGIN

House dust mite

House dust mite (HDM) is an important perennial allergen source and a significant cause of allergic rhinitis and asthma. Cross-reactivity between allergens present in HDM and invertebrates, such as shellfish and edible insects, is frequently described.[123,124]

Most cross-reactive reactions are believed to result from sensitization to tropomyosin.[10] Tropomyosin is a minor allergen in HDM (*Dermatophagoides pteronyssinus*, Der p 10), although often described as a major allergen in shellfish particularly in crustaceans (shrimp, lobster, crab), molluscs (mussels, oysters, scallops, octopus, squids, snails, abalones, clams, razor shell), and cockroaches.[125-136] Whether HDM immunotherapy can rarely induce shellfish allergy remains controversial with pros[137-139] and cons,[140] and might be related to differences in particular components (eg, tropomyosin) present in the immunotherapy preparations. Next to tropomyosin, also other allergenic components present in HDM and shellfish are able to cause cross-reactive reactions. Amongst them arginine kinase, myosin

light chain, sarcoplasmic calcium-binding protein, and hemocyanin are the most relevant.[123,141,142] Because of the extensive *in vitro* and *in vivo* cross-reactivity, allergy tests for the diagnosis of shellfish allergy should always be interpreted with caution, especially in HDM allergic patients. In a study of Thalayasingam et al,[143] it was demonstrated that 26.3% of HDM allergic patients tolerating shrimp showed false-positive sIgE antibodies to a shrimp extract. As a matter of fact, the clinical relevance of positive sIgE and/or SPT to shrimp varies from 13% to 67% depending on the inclusion criteria.[144-146] These numbers underline that a food challenge is essential in patients with an unclear history of allergic symptoms to shellfish, particularly in those patients with an HDM sensitization. Besides that, the literature does not support the recommendation to (preventively) avoid crustaceans, molluscs, or edible insects in HDM allergic patients.

Finally, patients with HDM allergy might also react directly to mite allergens in food. In the so-called pancake syndrome, patients might develop (severe) allergic reactions after ingestion of food containing mite-contaminated flour.[147,148]

CROSS-REACTIVE AEROALLERGENS OFF VERTEBRATE ANIMAL ORIGIN

The most relevant cross-reactions between food and aeroallergens from mammalian and avian origin are the "pork-cat syndrome" and the "bird-egg syndrome."

The "pork-cat syndrome" was reported for the first time in France and is an IgE-mediated reaction on porcine meat triggered by a primary sensitization to the serum albumin present in cat dander (*Felis domesticus,* Fel d 2). Overall, it has been estimated that 1% to 3% of patients sensitized to cat, mainly older children or adults, are at risk to develop allergic symptoms on ingestion of mainly raw pork.[149] In general, allergic symptoms occur immediately after consumption of pork meat and can range from mild allergic symptoms restricted to the oropharynx to severe generalized symptoms. The fact that symptoms appear soon after ingestion of the meat might be helpful in differentiating "pork-cat syndrome" from delayed anaphylaxis to red meat due to sensitization to alpha-gal. Serum albumins are heat labile, and therefore allergic reactions do most frequently occur on fresh meat or dried and smoked pork. Next to allergic symptoms on pork meat, some patients with the cat/pork syndrome do experience allergic symptoms on consumption of beef meat, chicken meat, and fresh milk.[150-152] Furthermore, also horse, dog, and hamster dander have been described as primary sensitizers for serum albumin—related meat allergy.[150,153,154]

In the "bird-egg syndrome," respiratory sensitization to bird allergens causes cross-reactive allergy symptoms on the ingestion of egg.[155] This syndrome is due to cross-reactivity between airborne bird serum proteins and serum albumins present in egg yolk (eg, *Gallus domesticus*, Gal d 5). Clinical symptoms reported on raw or soft boiled egg yolk are varying from oral and/or gastrointestinal symptoms to systemic reactions.[156] Typically, egg allergy starts in early childhood and is likely to be outgrown; however, egg allergy within the "bird-egg syndrome" oftentimes occurs at later age and is persisting.[157] Although cross-sensitization to poultry meat is common in patients with "bird-egg syndrome," true clinical reactions after meat ingestion are reported, but appear to be rare, probably because chicken meat is consumed well cooked and serum albumins are heat labile.[158] Actually, sensitization to egg-yolk proteins could also predispose some patients to respiratory symptoms from birds (egg-bird syndrome).[157] Finally, also reported is an "egg-egg syndrome," in which airborne egg proteins used in the occupational setting (bakery and confectionery industry) induced cross-reactivity to ingested eggs.[159]

DIAGNOSIS

Like for all IgE-mediated diseases, a diagnostic approach of (secondary) food allergy starts with a thorough clinical history with a main focus on the inhalant allergy and potential related cross-reactivities and should further be pieced together using different *in vitro* and *in vivo* tests. In general, clinical suspicion of the underlying inhalant allergy is easily documented using traditional extract-based skin tests and sIgE antibody assays. In contrast, correct diagnosis of the related food allergies is oftentimes more challenging and poses significant difficulties, mainly because of the poor specificity of the available tests. As described above, a positive skin test and/or sIgE results do not necessarily reflect genuine allergy but merely clinically irrelevant sensitization. Currently available diagnostic methods have only a limited predictive value for the outcome of oral provocation testing or the severity of a clinical reaction. The reason why some sensitizations do result in allergic symptoms and other sensitizations are clinically irrelevant is currently unknown; however, it has been hypothesized that this might depend on inhibitory mechanisms,[160] specific IgG4 response,[161] the affinity of IgE antibodies, and the valency of allergens.[162,163] Furthermore, the clinical outcome also depends on the amount of allergen and/or allergenicity of the allergen ingested, which has been described to depend on different factors such as the cultivation conditions, ripeness of the fruit, and postharvest storage.[164,165]

In many occasions, additional tests such as molecular diagnosis, BAT, and eventually food challenges might be required for correct diagnosis and also to avoid unnecessarily restrictive diets. However, it should be emphasized that even these diagnostics do not display absolute predictive values and not all are easily accessible for mainstream use. For example, molecular diagnostics have been demonstrated to be of little value to diagnose Bet v 1-related food allergies, as the technique fails to discriminate between patients sensitized to birch with and without cross-reactive food allergy.[14,46] Therefore, in a patient with allergic reactions to related plant foods containing cross-reactive allergens out of the same protein family, it is commonly sufficient to test a gatekeeper/only 1 member of this cross-reactive allergen family. Additional tests would only demonstrate more cross-reactions with questionable clinical relevance. Furthermore, CCD-free recombinant proteins can benefit the identification of clinically irrelevant sIgE originating from a sensitization to plant and invertebrate CCDs as frequently observed in sensitization to grass and weed pollen.[13]

BATs might, to some extent, be helpful in discriminating between patients with a clinically significant sensitization and patients who are merely sensitized, as it reflects a functional response rather than sensitization.[18,20] More studies are needed to validate BAT and to allow its entrance in mainstream use.

Finally, in cases of an unclear history or inconclusive tests, oral provocations are mandatory to correctly diagnose food allergic patients and give correct dietary advices.

TREATMENT

If the diagnosis of a food allergy due to cross-reactions is confirmed, elimination diets should be recommended. In this review, it has been repeatedly shown that inhalant allergens might cause positive tests to cross-reacting foods that might not have any clinical implication. Therefore, elimination diets should never be based on sensitization profiles only, and besides that, it is not recommended to preventively avoid potential cross-reactive food sources.

The acute management of a food allergy and treatment of the different inhalant allergies potentially responsible for a secondary food allergy are beyond the scope of this review. The decision to prescribe an epinephrine autoinjector should be based on risk stratification for the individual patient (eg, likelihood of a systemic reaction, comorbidities, sensitization profile, foods involved, ease of access to emergency treatment).[166]

Hitherto, the evidence for immunotherapy modifying the underlying inhalant allergy to be efficacious to treat the associated cross-reactivities is contradictory. Beneficial effects of allergen immunotherapy on pollen-related food allergies have been described.[167,168] However, these results could not be reproduced in other studies.[169-171] Therefore, at present secondary food allergies do not justify immunotherapy to cross-reactive inhalants.

GENERAL CONCLUSIONS

A significant part of all IgE-mediated food allergies results from sensitization to cross-reactive structures present in food and inhalant allergens. The clinical presentation of secondary food allergies can be very heterogeneous and vary between mild symptoms restricted to the oropharynx and severe generalized reactions, including life-threatening anaphylaxis. Correct diagnosis of these cross-reactive food allergies is not always straightforward, mainly because the available diagnostic tests do not have an absolute predictive value. As a matter of fact, cross-reactivity might severely hinder food allergy diagnosis, as positive tests to cross-reacting foods might not correctly predict safe consumption. Therefore, recognition of cross-reactive patterns and associated allergic symptoms is the cornerstone of correct diagnosis and is needed for correct interpretation of diagnostic tests. In cases of vague histories or inconclusive tests, oral provocations are indicated. If the diagnosis of a cross-reactive food allergy is confirmed, elimination diets should be recommended and an epinephrine autoinjector should be prescribed in severe cases.

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