

Food contact hypersensitivity syndrome: the mucosal contact urticaria paradigm

G. N. Konstantinou and C. E. H. Grattan

Dermatology Department, Norfolk and Norwich University Hospital, Norwich, UK

Summary

Oral allergy syndrome (OAS) or pollen–fruit allergy syndrome represents a mucosal allergic contact urticaria in people sensitized to common pollens, due to IgE cross-reactivity between homologous pollen allergens and various plant foods. It is the most prevalent food allergy, affecting millions of people with respiratory allergies. Usually, symptoms are mild, self-limiting and localized to the oropharyngeal mucosa, although they may sometimes become generalized and life-threatening. Although patients usually recognize the offending foods, diagnosis may sometimes be complicated. Several clinical syndromes and association between pollens and plant-derived foods have been described. Crossreactivity on the basis of stringent immunological and allergological criteria can also occur in people without pollen sensitization or concomitant respiratory allergies, as in latex–fruit syndrome. The term ‘food contact hypersensitivity syndrome’ (FCHS) is proposed in this paper for the first time, to include all mucosal hypersensitivity reactions presenting with contact to food (both immunological and nonimmunological), whether due to crossreactivity with homologous plant-derived allergens or not. At this time, prophylaxis and treatment can only be attained by avoidance, even when symptoms are mild, with consequent impairment in quality of life. A better understanding of the pathophysiological mechanisms of FCHS and food allergy in general is essential for deeper insights and future emergence of effective therapies.

Introduction

Many patients with respiratory allergies to common pollens (pollinosis) experience tingling, pruritus, erythema or angio-oedema of the lips, tongue and soft palate after contact of the oral cavity with a variety of plant-derived foods, but not after ingestion. These clinical features characterize oral allergy syndrome (OAS).¹ They may not be restricted to the oropharyngeal mucosa, but may also include the gastrointestinal, respiratory or even cardiovascular systems.

These symptoms are a type I hypersensitivity immunological analogue of a mucosal allergic contact urticaria reaction, caused by crossreactivity between homologous pollen and food allergens. Several syndromes have been described, such as birch–fruit, celery–mugwort–birch or celery–mugwort–spice.

‘Pollen–food allergy syndrome’ (PFAS) has been proposed as an alternative, more generic term to OAS, as OAS focuses on symptoms occurring in the oral cavity.² Crossreactivity on the basis of stringent immunological and allergological criteria can also occur in people without pollen sensitization, as in latex–fruit syndrome.³ Therefore, we propose the term ‘food contact hypersensitivity syndrome’ (FCHS), to include not only PFAS and latex–fruit syndrome but also all mucosal hypersensitivity reactions presenting with contact urticaria to food (both immunological or non-immunological), whether due to crossreactivity to

Correspondence: Dr George N. Konstantinou, Department of Dermatology, Norfolk and Norwich University Hospital, Norwich NR4 7UY, UK.
E-mail: georgenk@med.auth.gr

Conflict of interest: none declared.

Accepted for publication 11 February 2008



Figure 1 Food contact hypersensitivity syndrome includes all mucosal hypersensitivity reactions presenting with contact urticaria to food (both immunological or non-immunological), relevant to crossreactivity with homologous plant-derived allergens or not, in sensitized or non-sensitized individuals.

homologous plant-derived allergens or not, in sensitized or nonsensitized people. This terminology extends not only to crossreactivity between aeroallergens and nonplant foods, such as bird-egg syndrome⁴ and the unusual and curious association between house dust mites and snails,⁵ but also to both allergic and nonallergic contact urticaria (CU). For example, it can also include nonimmunological reactions (nonallergic CU) that may occur after contact with some foods containing histamine or other vasoactive amines (e.g. pineapple, red wine, aged cheeses, sauerkraut and pickled herring), or foods that may cause direct histamine release from mast cells without the presence of any specific IgE antibodies (e.g. tomato, strawberries, pineapple and alcohol)⁶ (Fig. 1).

Epidemiology and risk factors

Prevalence of FCHS is influenced by a great variety of factors and seems to on the increase, with a rising incidence in respiratory allergies. The most important of these factors are firstly, the type of sensitization and, secondly, the crossreactivity patterns (possibly genetically predisposed) in different geographical regions. The

most common sensitizations found among people with FCHS in central and north Europe are birch, grasses and mugwort pollens (Fig. 2), whereas in Mediterranean countries, sensitization to grasses, parietaria and ragweed pollens predominates. A review of 31 cases in Norwich showed 19% had specific sensitization to silver birch, 9% to grasses and 5% to mugwort, and 67% showed multiple sensitizations to these pollens, in keeping with the known prevalence in northern Europe. About 20% of sensitized residents in the Mediterranean region experience FCHS,⁷ and this rate rises up to 50% in the rest of Europe.⁸ Especially in central Europe, evidence from epidemiological studies suggests that evidence based FCHS occurs up to 10% of the general population, showing the emerging extent of the problem.⁹

In addition, naturally existing flora, the period of indigenous efflorescence, and dietary habits also play a critical role.¹⁰ The concentration and distribution of aeroallergens is also affected by prolonged and modified pollinating periods and by long-distance transport of anemophilous pollen (such as birch pollen grains), which may explain the increased sensitization among residents in areas thousands of miles from the pollen sources.¹¹ Onset and duration of the pollinosis period,



Figure 2 The three major sources of pollen related to oral allergy syndrome and their pollination periods for the UK and Eastern Europe (main picture shows complete plant; inset is detail of flowerhead). (a) *Betula pendula* (silver birch) flowers from the beginning of April until mid-May in eastern European countries while pollen concentration generally peaks during mid-April. Main figure of tree and foliage, inset showing the catkin. (b) *Artemisia vulgaris* (mugwort) is a native weed in waste places, waysides and hedgerows. Although it is able to survive in both cool, dry and in warm, wet conditions, its pollination period is quite short, lasting from mid July until the end of August with a peak period during mid-August. Inset shows detail of its small flowers. (c) Timothy grass (*Phleum pratense*) grows on sandy, loamy soils throughout Europe except the Mediterranean region. Its flowering period starts at the beginning of May and lasts until September. The highest air pollen counts can normally be expected during mid-June.

Pathophysiology and clinical implications

Immunology

Circulating IgE antibodies, specific to common pollens (sIgE), crossreact with structural (identical amino acid sequence in one or several epitopes) and functional (antigenic and allergenic properties) homologous plant-derived food allergens after contact with the oral cavity.¹² These sIgE-allergen complexes are bound to the surface of mucosal mast cells and basophils, which release histamine, cytokines and inflammatory mediators locally. Sensitization to pollen allergens antedates and leads to induction of sIgE, which afterwards crossreacts with homologous food allergens.^{12,13}

Crossreactive allergens

Profilins (ubiquitous pan-allergens in plants, e.g. Api g 4 in celery) and allergens homologous to pathogenesis-related type 10 (PR-10) proteins (e.g. Bet v 1, the major allergen of birch pollen) are the two major plant-allergen families responsible for the majority of these interactions.¹⁴ Lipid-transfer proteins (LTPs) comprise another important group of allergens, generally located in the peel of many fruits (such as peach and plum). Although LTPs are usually responsible for class 1 food allergies (in contrast with class 2 food allergies in which the immunological basis is IgE crossreactivity) they can also demonstrate crossreactivity with pollens.¹⁵

Several clinical syndromes and associations between pollens and plant derived foods have been described. Birch pollen crossreactivity with apple, cherry, pear (*Rosaceae* fruits) or celery and carrot (*Apiaceae* vegetables) are the most common. Crossreactivity can also

and therefore exposure and sensitization, may also be explained by environmental factors such as climate change and extreme meteorological conditions.

occur in people without pollen sensitization and respiratory allergies. Characteristic examples are the bird-egg syndrome (crossreactivity due to homologous allergens found in chicken feathers and egg yolk),⁴ the mites-snails association (crossreactivity due to tropomyosin),⁵ and the latex-fruit syndrome (crossreactivity related to profilins)^{3,16} which are molecularly and immunologically comparable with pollen-plant-derived-food cross-reactivity. Table 1 presents the most common clinically related crossreactions.

Effects of heat and digestion

The allergenicity (IgE binding affinity) of most plant-derived molecules is highly dependent on their tertiary structure. Thermal processing and exposure to gastrointestinal proteases degrade these allergens substantially and irreversibly, abolishing their IgE-binding capacity immediately.^{17,18} Thus, consumption of well-cooked plant-related foods (> 80 °C for a few minutes) may be tolerated clinically, although this seems not always to be the case and might explain why cooked celery¹⁹ and roasted hazelnuts²⁰ can still sometimes induce clinically important reactions.

Although tertiary structure may be susceptible to cooking and digestion, the primary protein structure, which is responsible for T cell-mediated reactions, is not affected. Thus T-cell crossreactivity may still occur and explain, for instance, exacerbations of atopic eczema (AE) in children and adults with respiratory allergies and specific cutaneous crossreactive T cells, even in the absence of immediate FCHS-related symptoms.^{21,22}

Clinical features

Most patients who report FCHS-related symptoms (mainly adults) have respiratory allergies (hay fever and/or asthma) or are at least sensitized to one of the FCHS-related pollens.²³ Characteristic and specific for this entity are oropharyngeal sensations of pruritus, tingling and burning, which are sometimes accompanied by angio-oedema of the lips, oral mucosa, soft palate or tongue, during or shortly after eating raw or uncooked pollen-related foods. At the same time, the patient may experience hay-fever exacerbation, with watery itchy eyes, runny nose and sneezing. Handling the raw fruit or vegetable, peeling it or even touching the juice may cause the same symptoms or cause erythema and contact urticaria of the contaminated skin.^{23,24}

Symptoms resolve promptly after food is swallowed, due to rapid proteolytic denaturation by the gastro-

intestinal enzymes. Prior heating of the food is prophylactic for most allergens,^{14,17,18} with the exception of nuts²⁰ and sometimes celery.¹⁹ Patients with FCHS and AE may experience eczema exacerbation after consuming even cooked pollen-related foods.^{18,21,22}

Uncommonly, gastrointestinal symptoms such as cramps, nausea, vomiting or diarrhoea can occur. Rarely, life-threatening reactions have been reported, with angio-oedema of the throat, wheezing, respiratory distress or anaphylactic shock.^{19,23,25} Severe reactions to most of these cases were attributed to cross-sensitization with LTPs.^{10,15}

FCHS-related symptoms can occur perennially but may be more severe during or after the responsible pollen period (Fig. 2), due to an increase of specific IgE levels and inflammatory mediator release.

Diagnosis





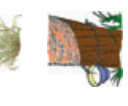
The diagnostic approach should always start with an explicit medical history and physical examination. Evidence of respiratory allergies (hay fever or/and asthma during a specific pollen season) and history of symptoms consistent with FCHS provide high positive and negative predicted values in diagnosis.²⁶ Interestingly, these symptoms are seldom described unless they are very severe or prompted appropriately during the medical history.

Secondly, sensitization to the main FCHS-related pollens should be evaluated using *in vitro* [specific IgE with radioallergosorbent testing (RAST) or ImmunoCAP] or/and *in vivo* methods [skin-prick testing (SPT) and nasal provocation tests when needed]. Afterwards, pollen sensitization results should be correlated with the relevant foods from the case history that are known to crossreact (Table 1).

Sensitization to the plant foods in question should be confirmed, preferably with the prick to prick procedure (a lancet is pricked into the fresh/raw foods in question and then into the skin) which is practical and safe, although not standardized.²⁶ The majority of plant-derived proteins are difficult to extract and highly labile, and therefore diagnostic setups using commercially available extracts for *in vitro* (RAST) or *in vivo* (common commercial SPTs) assays are in many cases unsatisfactory.²⁷ One solution to this problem would be the use of standardized recombinant food allergens.²⁸

Although *in vivo* and *in vitro* tests provide high specificity and sensitivity, they do not necessarily predict clinical reactions, thus oral food challenges may have to be considered when the history cannot provide enough information for the responsible foods (mixed food

Table 1 Food contact hypersensitivity syndromes (s.) and associations (as.) between pollen or latex and plant-derived food with clinically correlated crossreactivity

	Food contact hypersensitivity syndromes	Crossreacting foods frequency	
		Frequent	Infrequent but possible
Pollen			
Birch	Celery–mugwort–birch syndrome, birch–celery syndrome or birch–fruit syndrome	Apple, pear, carrot, celery, tomato, cherry	Plum, cherry, nectarine, peach, rest Apiaceae* species, mango, banana, strawberries, lychee, orange, potato, soy bean, sunflower, bell peppers, paprika, hazelnut, chestnut, peanut
 <i>Artemisia vulgaris</i>	Celery–mugwort–spice syndrome, mugwort–peach association, mugwort–mustard syndrome, mugwort–chamomile association, celery–birch–mugwort syndrome	Carrot, celery, aniseed, peach	Rest of the Apiaceae* species, bell pepper, paprika, mango, garlic, onion, leek, broccoli, cauliflower, chestnut, apple, nectarine, mustard, broccoli, cabbage, chamomile
 <i>Ambrosia artemisiifolia</i>	Ragweed–melon–banana association	Melon	Apple, banana, watermelon, cucumber, courgette, celery, sunflower
 <i>Chenopodium album</i>	Goosefoot–fruit association	Banana, melon, peach	Nectarine, asparagus, celery, kiwi, potato, olive, garlic, onion, leek
 Timothy grass (<i>Phleum pratense</i>)			Apple, lychee, tomato, celery, corn, bell pepper, paprika
 Latex	Latex–fruit syndrome	Avocado, banana, chestnut, kiwi fruit, mango, melon, fig, papaya, tomato	Celery, passion fruit, peanut, potatoes, pineapple, peach

* Apiaceae botanical family: celery, coriander, aniseed, fennel, caraway, dill, carrot, parsley, cumin.

products, 'junk' food) or is not typical of FCHS (symptoms persisting for hours, heating does not eliminate them) or when sensitization to either pollens or respective foods has not been proven.

The procedure includes initial contact of the fresh/raw food with the lips and oral mucosa, chewing for a couple of minutes and then spitting out the food. If any of the described symptoms occur within 15 min, the challenge is positive. Double-blind placebo-controlled food challenges are considered the gold standard in food allergies, but are impractical in suspected FCHS because the fresh material has to be masked and should not be swallowed immediately. Precautions should be always taken to treat serious reactions during food challenges when systemic symptoms have been reported or suspected.

Differential diagnosis

Although the medical history is characteristic in most cases, it is important to differentiate between IgE- and non-IgE-mediated FCHS conditions or other diseases. Severe systemic reactions or absence of pollen sensitization suggest classic food allergy irrelevant to cross-reactivity. Eosinophilic oesophagitis, in which a similar pathogenesis has been proposed,²⁹ or gastrointestinal reflux disease can also present with complaints from the throat. However, food impaction, dysphagia and prolonged upper gastrointestinal complaints predominate. Allergic or irritant contact dermatitis to spices, garlic, acidic foods or additives should also be excluded.

Management

Most patients are aware of their condition and avoid the offending foods themselves. The general recommendation and treatment of FCHS is avoidance of the relevant foods, even if symptoms are mild. Many patients can tolerate cooked, baked, microwaved, dried, unripe, partially ripe or peeled fruits. In these patients, consumption of these forms may be allowed unless systemic reactions or exacerbations of AE have previously been reported. Prior antihistamine administration is not recommended; although it may reduce, but not resolve, symptoms, it may also mask potential progressively worsening systemic reactions.³⁰

Provided that a pollen allergen is responsible for the crossreactivity with a food allergen, it might be expected that specific immunotherapy to this pollen could eliminate FCHS-related symptoms. This is still under consideration, as results from various trials using subcutaneous or sublingual immunotherapy are controversial.^{31–33}

When a systemic reaction occurs for the first time or after previous localized oropharyngeal reactions, careful evaluation should also include all potential cross-reactive foods. Until then, an elimination diet should include all relevant food products. In addition, patients should be educated how and when to use appropriate rescue medication such as antihistamines and epinephrine, which they should always carry with them.

Specific precautions should be taken for patients with FCHS on ulcer-healing drugs. There is evidence suggesting that antiulcer treatment (H₂-receptor blockers and proton pump inhibitors) primes *de novo* IgE formation to numerous digestion-labile dietary compounds including FCHS-related food allergens.^{34,35} Although not yet proved, this might increase the risk of more severe or systemic reactions in these patients.

References

- 1 Amlot PL, Kemeny DM, Zachary C *et al*. Oral allergy syndrome (OAS): symptoms of IgE-mediated hypersensitivity to foods. *Clin Allergy* 1987; **17**: 33–42.
- 2 Kelso JM. Pollen-food allergy syndrome. *Clin Exp Allergy* 2000; **30**: 905–7.
- 3 Brehler R, Theissen U, Mohr C, Luger T. 'Latex-fruit syndrome': frequency of cross-reacting IgE antibodies. *Allergy* 1997; **52**: 404–10.
- 4 Quirce S, Maranon F, Umpierrez A *et al*. Chicken serum albumin (Gal d 5*) is a partially heat-labile inhalant and food allergen implicated in the bird-egg syndrome. *Allergy* 2001; **56**: 754–62.
- 5 Vuitton DA, Rance F, Paquin ML *et al*. Cross-reactivity between terrestrial snails (*Helix* species) and house-dust mite (*Dermatophagoides pteronyssinus*). I. *In vivo* study. *Allergy* 1998; **53**: 144–50.
- 6 Bahna SL. Adverse food reactions by skin contact. *Allergy* 2004; **59** (Suppl. 78): 66–70.
- 7 Cuesta-Herranz J, Lazaro M, Figueredo E *et al*. Allergy to plant-derived fresh foods in a birch- and ragweed-free area. *Clin Exp Allergy* 2000; **30**: 1411–6.
- 8 Bircher AJ, Van Melle G, Haller E *et al*. IgE to food allergens are highly prevalent in patients allergic to pollens, with and without symptoms of food allergy. *Clin Exp Allergy* 1994; **24**: 367–74.
- 9 Osterballe M, Hansen TK, Mortz CG, Bindslev-Jensen C. The clinical relevance of sensitization to pollen-related fruits and vegetables in unselected pollen-sensitized adults. *Allergy* 2005; **60**: 218–25.
- 10 Fernandez-Rivas M, Bolhaar S, Gonzalez-Mancebo E *et al*. Apple allergy across Europe: how allergen sensitization profiles determine the clinical expression of allergies to plant foods. *J Allergy Clin Immunol* 2006; **118**: 481–8.
- 11 Sofiev M, Siljamo P, Ranta H, Rantio-Lehtimäki A. Towards numerical forecasting of long-range air transport

- of birch pollen: theoretical considerations and a feasibility study. *Int J Biometeorol* 2006; **50**: 392–402.
- 12 Valenta R, Kraft D. Type 1 allergic reactions to plant-derived food: a consequence of primary sensitization to pollen allergens. *J Allergy Clin Immunol* 1996; **97**: 893–5.
 - 13 Kazemi-Shirazi L, Pauli G, Purohit A *et al.* Quantitative IgE inhibition experiments with purified recombinant allergens indicate pollen-derived allergens as the sensitizing agents responsible for many forms of plant food allergy. *J Allergy Clin Immunol* 2000; **105**: 116–25.
 - 14 Breiteneder H, Ebner C. Molecular and biochemical classification of plant-derived food allergens. *J Allergy Clin Immunol* 2000; **106**: 27–36.
 - 15 Lombardero M, Garcia-Selles FJ, Polo F *et al.* Prevalence of sensitization to Artemisia allergens Art v 1, Art v 3 and Art v 60 kDa. Cross-reactivity among Art v 3 and other relevant lipid-transfer protein allergens. *Clin Exp Allergy* 2004; **34**: 1415–21.
 - 16 Yagami T. Allergies to cross-reactive plant proteins. Latex-fruit syndrome is comparable with pollen-food allergy syndrome. *Int Arch Allergy Immunol* 2002; **128**: 271–9.
 - 17 Ballmer-Weber BK, Hoffmann A, Wuthrich B *et al.* Influence of food processing on the allergenicity of celery: DBPCFC with celery spice and cooked celery in patients with celery allergy. *Allergy* 2002; **57**: 228–35.
 - 18 Bohle B, Zwolfer B, Heratizadeh A *et al.* Cooking birch pollen-related food: divergent consequences for IgE- and T cell-mediated reactivity *in vitro* and *in vivo*. *J Allergy Clin Immunol* 2006; **118**: 242–9.
 - 19 Ballmer-Weber BK, Vieths S, Luttkopf D *et al.* Celery allergy confirmed by double-blind, placebo-controlled food challenge: a clinical study in 32 subjects with a history of adverse reactions to celery root. *J Allergy Clin Immunol* 2000; **106**: 373–8.
 - 20 Hansen KS, Ballmer-Weber BK, Luttkopf D *et al.* Roasted hazelnuts - allergenic activity evaluated by double-blind, placebo-controlled food challenge. *Allergy* 2003; **58**: 132–8.
 - 21 Reekers R, Busche M, Wittmann M *et al.* Birch pollen-related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. *J Allergy Clin Immunol* 1999; **104**: 466–72.
 - 22 Breuer K, Wulf A, Constien A *et al.* Birch pollen-related food as a provocation factor of allergic symptoms in children with atopic eczema/dermatitis syndrome. *Allergy* 2004; **59**: 988–94.
 - 23 Ortolani C, Pastorello EA, Farioli L *et al.* IgE-mediated allergy from vegetable allergens. *Ann Allergy* 1993; **71**: 470–6.
 - 24 Eriksson NE, Formgren H, Svenonius E. Food hypersensitivity in patients with pollen allergy. *Allergy* 1982; **37**: 437–43.
 - 25 Kleine-Tebbe J, Vogel L, Crowell DN *et al.* Severe oral allergy syndrome and anaphylactic reactions caused by a Bet v 1-related PR-10 protein in soybean, SAM22. *J Allergy Clin Immunol* 2002; **110**: 797–804.
 - 26 Anhoj C, Backer V, Nolte H. Diagnostic evaluation of grass- and birch-allergic patients with oral allergy syndrome. *Allergy* 2001; **56**: 548–52.
 - 27 Vieths S, Hoffmann A, Holzhauser T *et al.* Factors influencing the quality of food extracts for *in vitro* and *in vivo* diagnosis. *Allergy* 1998; **53**: 65–71.
 - 28 Bohle B, Vieths S. Improving diagnostic tests for food allergy with recombinant allergens. *Methods* 2004; **32**: 292–9.
 - 29 Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001; **107**: 83–90.
 - 30 Bindslev-Jensen C, Vibits A, Stahl Skov P, Weeke B. Oral allergy syndrome: the effect of astemizole. *Allergy* 1991; **46**: 610–3.
 - 31 Asero R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. *Clin Exp Allergy* 1998; **28**: 1368–73.
 - 32 Bucher X, Pichler WJ, Dahinden CA, Helbling A. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. *Allergy* 2004; **59**: 1272–6.
 - 33 Kinaciyan T, Jahn-Schmid B, Radakovics A *et al.* Successful sublingual immunotherapy with birch pollen has limited effects on concomitant food allergy to apple and the immune response to the Bet v 1 homolog Mal d 1. *J Allergy Clin Immunol* 2007; **119**: 937–43.
 - 34 Scholl I, Untersmayr E, Bakos N *et al.* Antiulcer drugs promote oral sensitization and hypersensitivity to hazelnut allergens in BALB/c mice and humans. *Am J Clin Nutr* 2005; **81**: 154–60.
 - 35 Untersmayr E, Bakos N, Scholl I *et al.* Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. *FASEB J* 2005; **19**: 656–8.