

Educational Clinical Case Series

Allergies to fruits and vegetables

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Allergic reactions to fruits and vegetables are frequently observed in older children and adolescents. They can result from a primary sensitization to food allergens or from a primary sensitization to inhalant allergens such as pollens or latex. In the case of fruit allergies, the stability of the allergens involved is crucial to the sensitization pathway and in the clinical presentation of the food allergy. Two patients allergic to fruits are presented and discussed in the light of the allergens involved. Patient 1 was a 14 yr-old girl with a grass and olive pollen allergy who developed oropharyngeal symptoms typical of the oral allergy syndrome (OAS) with multiple fruits from taxonomically unrelated families, and who was sensitized to profilin. Patient 2 was an 8 yr-old girl, with no pollen allergies, who developed systemic reactions to peach and apple, and who was sensitized to non-specific lipid transfer proteins (LTP). Profilins are labile allergens present in pollens and foods, and sensitization occurs through the respiratory route to pollen profilin. The cross-reactive IgE antibodies generated can elicit local reactions in the oropharyngeal mucosa (OAS) when exposed to fruit profilins. In contrast, LTPs are a family of stable allergens that resist thermal treatment and enzymatic digestion, and can thus behave as true food allergens inducing primary (non-pollen related) sensitizations and triggering systemic reactions. These two cases represent two distinct patterns of sensitization and clinical expression of fruit allergies that are determined by the panallergens involved (LTPs and profilins) and their intrinsic physicochemical properties. Additionally, these two cases also show the improved diagnostic value of Component Resolved Diagnosis, and strengthen its utility in the routine diagnosis and management of patients.

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Cow's milk and hen's egg are the foods most commonly involved in allergic reactions in infants and children below 3 yr (1). Allergic reactions to plant foods are infrequent in this age group, but their prevalence increases with age becoming the most frequent foods inducing allergic reactions in older children and adults. The relative importance of different plant foods varies among countries, possibly in relation (among other factors) to local dietary habits and pollen exposures. Peanut, followed by tree nuts, are the plant foods most commonly involved in allergic reactions in the USA and

United Kingdom (1–4). In Central and Northern Europe (especially in areas rich in birch trees), and in the Mediterranean, the prevalence of peanut allergy decreases but tree nuts (mainly hazelnut, followed by walnut) and fruits – especially those belonging to the *Rosaceae* family (including apple, peach and pear), and kiwi – emerge as important food allergies. Vegetables are uncommonly involved in allergic reactions in children (5–8). Data of a recent cross-sectional survey – *Alergológica 2005* (9) performed in Spain amongst 4991 patients first seen in allergy clinics throughout the country has shown a

prevalence of food allergy of 7.4%, with fresh fruits the most commonly involved allergens (in one third of reactions), whereas vegetables were only responsible of 7% of all food allergies. Fresh fruits were the most frequent cause of food allergy in patients over 5 yr of age, and *Rosaceae* fruits were the most commonly involved.

It is currently accepted that allergy to fruits and vegetables can result from a primary sensitization to food allergens or from primary sensitization to pollens or latex. The physico-chemical properties of the food allergens involved, and, especially, their resistance to proteolysis in the digestive tract, seem to be decisive in the sensitization pathway and in the elicitation of symptoms (10, 11). The stability to proteases is considered a key factor to induce direct sensitizations through the oral route, as well as systemic reactions upon ingestion (complete allergens, class one food allergy) (12, 13). An example is allergy to non-specific lipid transfer proteins (LTPs) (11, 14). In contrast, the labile allergens that do not resist the digestion process seem not to be able to induce direct sensitization through the oral route, but they can elicit symptoms in the oral mucosa on ingestion. In these cases the primary sensitization occurs via the respiratory tract to a homologous protein present in an inhalant, and the food allergy appears later as a consequence of IgE cross-reactivity (incomplete allergens, class two food allergy) (10–13). This is the case of plant food allergies linked to birch pollen allergy (10, 11).

There is some confusion with the term oral allergy syndrome (OAS). In this manuscript OAS refers to the oropharyngeal symptoms that appear shortly following the ingestion of any food and consist of pruritus of the lips, tongue, palate, ears, and throat; mild angioedema at the same sites may be associated (10, 15). The term OAS has also been used to refer to any reaction induced by plant foods in pollen allergic patients (16), but as systemic involvement can be observed in these subjects, even in the absence of oral symptoms, the term pollen-food allergy seems more adequate (17). Furthermore, oral symptoms can be elicited by any type of food, of plant or animal origin, linked or not to allergies to inhalants or latex (15).

In this paper we report and discuss two children allergic to fruits included in the *Vegetalia* study, who represent the two different patterns of food allergy mentioned above. *Vegetalia* is a multicenter cross-sectional survey that aimed to study plant food allergies across Spain at the clinical and molecular level (18). A comprehensive evaluation that included

Table 1. Standard panel for skin prick tests (SPT) in the *Vegetalia* study

Pollens
Grass (mixture)
Olive (<i>Olea europaea</i>)
Cypress (<i>Cupressus spp</i>)
Plane tree (<i>Platanus acerifolia</i>)
Mugwort (<i>Artemisia vulgaris</i>)
Pellitory (<i>Parietaria judaica</i>)
English plantain (<i>Plantago lanceolata</i>)
Russian thistle (<i>Salsola kali</i>)
Lamb's quarter (<i>Chenopodium album</i>)
Birch (<i>Betula verrucosa</i>)
Latex (<i>Hevea brasiliensis</i>)
Plant foods
Extracts
Peach
Melon
Lentil
Soybean
Mustard
Almond
Hazelnut
Walnut
Chestnut
Peanut
Sunflower seed
Fresh foods
Kiwi
Apple (<i>Golden delicious</i>)
Tomato
Banana
Controls
Saline
Histamine hydrochloride 10 mg/ml

All the SPT extracts were provided by ALK-Abelló (Madrid, Spain).

medical history, skin prick tests (SPT) to a panel of pollens, plant foods and latex (Table 1), determination of specific IgE to individual pollen and plant food allergens by the ADVIA Centaur[®] (Deerfield, IL, USA) (19) (Table 2), and oral food challenges (if needed), was performed in all subjects.

Case 1: oral allergy syndrome to fruits in a pollen allergic child

A 14 yr-old girl was referred by her pediatrician because of seasonal respiratory symptoms. Since the age of 6 she had presented in May and June with rhinoconjunctival symptoms, and in the last 2 yr during May she had noticed nocturnal and exercise-induced cough without associated wheezing or dyspnoea. She had been treated with oral antihistamines and inhaled disodium cromoglycate. Since the age of 10 she had experienced oropharyngeal itching, sometimes associated with throat hoarseness and lip erythema and oedema after eating melon, watermelon, kiwi, peach, apple, apricot, pear,

Table 2. Standard panel of pollen and plant food allergens for serum specific IgE determinations (ADVIA centaur®) in the *Vegetalia* study

Allergens tested <i>in vitro</i> by the ADVIA centaur®	
<i>Phleum pratense</i>	nPhl p 1 nPhl p 5
<i>Olea europaea</i>	nOle e 1 rOle e 9
<i>Cupressus sempervirens</i>	nCup s 1
<i>Platanus acerifolia</i>	rPla a 1 + nPla a 2
<i>Artemisia vulgaris</i>	nArt v 1
<i>Parietaria judaica</i>	nPar j 1
<i>Plantago lanceolata</i>	nPla l 1
<i>Salsola kali</i>	nSal k 1
<i>Chenopodium album</i>	rChe a 1 (Ole e 1 like) rChe a 3 (polcalcin)
PR-10 proteins (from birch pollen and apple)	nBet v 1 + rMal d 1
Profilins (from apple, melon and <i>Chenopodium</i>)	rMal d 4 + rCuc m 2 + rChe a 2
LTPs (from peach as family marker)	rPru p 3
Chitinases (from avocado and chestnut)	nPrs a 1 + rCas s 5
Lentil 7S globulin	nLen c 1
Mustard 2S albumin	nSin a 1
Cross-reactive carbohydrate determinants (CCDs)	Peroxidase

Specific IgE determinations were carried out by the ADVIA centaur® (Bayer HealthCare Diagnostics Division) immunoassay system developed by ALK-Abelló (19). Allergens were obtained from ALK-Abelló (Madrid, Spain), Facultad de Químicas of Universidad Complutense (Madrid, Spain), Escuela Técnica Superior de Ingenieros Agrónomos (Madrid, Spain) and Bial-Aristegui (Bilbao, Spain).

strawberry, banana, orange, and tangerine. The symptoms appeared in <5 min following the ingestion of these fruits, and were elicited by the fresh fruit. She had subsequently tolerated commercial apple and peach juices, and peach in syrup. As the oropharyngeal symptoms were mild, and subsided spontaneously in <15 min, the patient had presented with repeated oral reactions with the reported fruits, but had never had gastro-intestinal or respiratory complaints, nor generalized cutaneous involvement. The reactivity to peach and apple was confirmed by double-blind placebo-controlled food challenges (DBPCFC).

Skin prick test to pollens were all positive with the exception of pellitory (Table 3), although the patient only had symptoms during May and June which is the grass and olive pollen season in Madrid. Specific IgE determinations to individual pollen allergens revealed only positive results to the major allergens of grass (nPhl p 1 and 5), olive (rOle e 1) and cypress (nCup s 1), and to profilin (Table 5). The lack of response to the major allergens of the remaining pollens that induced positive SPT exclude primary sensitization to them, and the skin responses to them are

Table 3. Results of skin prick tests (SPT) with pollens and latex

	Case 1 (mm)	Case 2 (mm)
Grass (mixture)	9.5	0
Olive	11.5	0
Cypress	4.5	0
Plane tree	6.5	0
Mugwort	3	0
Pellitory	0	0
English plantain	3.5	0
Russian thistle	7.5	0
Lamb's quarter	3	0
Birch	6.5	0
Latex	0	0
Saline (negative control)	0	0
Histamine (positive control)	7	5

Mean wheal diameter is given. SPT ≥ 3 mm were considered positive.

explained by profilin sensitization. Similar discrepancies were observed between the SPT to plant foods (Table 4) and the serum IgE responses to the major plant food allergens (Table 5). This girl exhibited positive SPT to the fruits involved in adverse reactions, and to other plant foods (peanut, tree nuts, lentil, soybean and sunflower seed) (Table 4) that were well tolerated. However, she turned out to be

Table 4. Results of skin prick tests with plant foods

	Case 1 (mm)	Case 2 (mm)
Extracts		
*Peach	0	9
*Melon	8.5	0
*Lentil	4.75	0
*Soybean	3	0
*Mustard	5.25	0
*Almond	5.75	0
*Hazelnut	5	0
*Walnut	4.25	0
*Chestnut	6.25	0
*Peanut	5	0
*Sunflower seed	5.25	0
Fresh fruits		
*Kiwi	10.75	0
*Apple	Peel 5 Pulp 9	Peel 20 Pulp 6
*Tomato	8	0
*Banana	4	0
Melon	10	Nd
Watermelon	6.5	Nd
Peach	Peel 5 Pulp 9	Peel 18 Pulp 5
Pear	Peel 5 Pulp 6	Peel 3 Pulp 3
Strawberry	9.75	Nd
Orange	6	Nd
Tangerine	5	Nd

Mean wheal diameter is given. SPT ≥ 3 mm were considered positive.

* *Vegetalia* study standard panel; Nd, not done.

Table 5. Specific IgE determinations to individual pollen and plant food allergens (ADVIA centaur®)

Specific IgE determinations by ADVIA centaur®		Case 1 (kU/l)	Case 2 (kU/l)
<i>Phleum pratense</i>	nPhl p 1	96.84	0.0
	nPhl p 5	79.82	0.0
<i>Olea europaea</i>	nOle e 1	41.67	0.0
	rOle e 9	0.05	0.0
<i>Cupressus sempervirens</i>	nCup s 1	9.97	0.19
<i>Platanus acerifolia</i>	rPla a 1 + nPla a 2	0.02	0.0
<i>Artemisia vulgaris</i>	nArt v 1	0.21	0.06
<i>Parietaria judaica</i>	nPar j 1	0.01	0.03
<i>Plantago lanceolata</i>	nPla l 1	0.03	0.03
<i>Salsola kali</i>	nSal k 1	0.3	0.01
<i>Chenopodium album</i>	rChe a 1	0.03	0.0
	rChe a 3	0.04	0.0
PR-10 proteins	nBet v 1 + rMal d 1	0.27	0.0
Profilins	rMal d 4 + rChe a 2 + rCuc m 2	8.33	0.0
LTPs	rPru p 3	0.05	12.97
Chitinases	nPrs a 1 + rCas s 5	0.0	0.0
Lentil 7S globulin	nLen c 1	0.01	0.07
Mustard 2S albumin	nSin a 1	0.0	0.0
CCDs	Peroxidase	0.09	0.0

Values ≥ 0.35 kU/l were considered positive (shown in bold).

negative to all the major plant food allergens when tested for specific IgE (Table 5) which exclude primary food sensitization, and thus the extensive positivity in SPT to plant foods is related to sensitization to profilin, a panallergen found in pollens and plant foods (20). Furthermore, the clustering of food reactivities of our patient – *Rosaceae*, kiwi, banana, orange and tangerine, and *Cucurbitaceae* – has already been described as typically associated with profilin sensitization (21). Therefore, this case shows that specific IgE to profilin may lead to a misinterpretation of SPT (or serum IgE tests) performed with whole pollen and plant food extracts, that it is only uncovered by component resolved diagnosis (CRD).

The time course of the pollen and food allergies and the specific IgE responses to individual allergens in this patient suggest a primary sensitization through the inhalation route to pollens with the generation of cross-reactive IgE to pollen profilin. In a second step, the exposure to fruit profilin through the oral route induces reactions restricted to the oropharyngeal mucosa because of the lability of profilin to proteolysis (22, 23). Furthermore, profilin lability also explains why the reactions were only induced by fresh fruits and that processed fruits such as commercial fruit juices and peach in syrup were tolerated.

A similar pathogenesis and clinical presentation is found in plant food allergies linked to

birch pollen and related to sensitization to Bet v 1 and its homologous labile proteins in foods (10, 11, 24). The lability of Bet v 1 homologues (especially) and profilin involved in pollen-food allergies accounts for a low sensitivity of commercial food extracts used for SPT and serum IgE tests. Therefore SPT with fresh foods by the prick-prick technique should always be performed if a negative result is obtained with a commercial extract, as it is the case of peach in this patient.

As shown by this case and discussed above, the clinical presentation of plant food allergies related to profilin is mild, and restricted to the oropharyngeal area (11, 23, 25, 26). The natural history of the pollen-food allergies has not been analyzed in longitudinal studies but they are presumed to be as persistent as the pollen allergy they are linked to. Symptoms are mild and transient and resolve spontaneously, and therefore there is no need for treatment. Patients should be advised to avoid the fresh fruits, and those who react to just a few can easily find alternatives. However, compliance is sometimes poor because the symptoms are so mild that do not prevent patients from ingestion. Nutritional advice should be considered in those subjects who react to multiple fresh fruits with intense OAS. Cooked fruits are generally well tolerated and are permitted for patients as the thermolabile profilin loses its allergenicity. Immunotherapy can be a therapeutic option in these subjects, but there are no studies performed so far in profilin allergic patients. The role of pollen immunotherapy has only been investigated in apple and hazelnut allergies linked to birch pollen allergy and due to sensitization to Bet v 1 homologues (27–30). None of the clinical trials performed so far are double-blind placebo-controlled and only a few include DBPCFC to monitor efficacy. The results are controversial, and the beneficial effect observed in some studies seems to be transient as patients develop OAS months after having stopped birch pollen immunotherapy.

Case 2: systemic reactions to fruits in a child without associated pollen allergies

An 8 yr-old girl, with a previous history of mild atopic dermatitis, was referred by her pediatrician because of adverse reactions to fruits. At the age of 3 yr she first presented with an episode of oropharyngeal itching and facial erythema followed by facial angioedema, in the 15–30 min following the ingestion of a commercial peach juice. Symptoms subsided spontaneously without treatment. One week later she presented with a

similar reaction again after the intake of a commercial peach juice. Her mother had previously noticed contact urticaria with peach peel when the child handled fresh peach, but she had tolerated the ingestion of peeled peach. After the second reaction to peach juice, peach was withdrawn from her diet. At the age of seven she presented with oropharyngeal itching, facial erythema, and a mild urticaria that subsided spontaneously. This happened after the second bite to a fresh apple eaten with the peel, and since then she had eaten fresh apple pulp several times with good tolerance, although on one occasion she noticed mild oral itching. At the age of eight, 10 days before the first visit to our clinic, she ate a peeled apple in the school canteen, and went out to the playground. Approximately 30 min later she presented a generalized severe urticaria that needed emergency room treatment with antihistamines and steroids. She did not present with either respiratory or gastro-intestinal symptoms. She had no history suggestive of asthma or rhinoconjunctivitis.

This child had negative SPT to pollens and latex (Table 3), and negative serum IgE to individual pollen allergens (Table 5). She only had positive SPTs to peach, apple, and pear, which all belong to the *Rosaceae* family (Table 4). When the IgE response to individual plant foods was analyzed it turned out that she was only sensitized to Pru p 3, the peach LTP (Table 5). Therefore, this is a patient with no pollen allergies, who presented systemic reactions to the *Rosaceae* fruits peach and apple, and was exclusively sensitized to Pru p 3, the peach LTP and major allergen of this fruit in the Spanish population (31).

Lipid transfer proteins are a family of proteins with a compact structure stabilized by four disulphide bridges, that confer them a high stability (14, 22, 23) and thus the potential to induce primary sensitizations (non-pollen related) and systemic reactions on ingestion (11, 31, 32). The time course of the fruit allergies in this child suggest a primary sensitization to Pru p 3 with the generation of cross-reactive IgE. The apple allergy arises later as a result of the homology between Pru p 3 and Mal d 3, the apple LTP. Previous studies support the role of Pru p 3 as the primary sensitizer in allergy to LTPs (11, 33). Primary sensitization to peach LTP may result from exposure through the oral route, although the skin contact may be relevant as well to induce IgE responses. Contact urticaria is commonly observed in patients allergic to peach (26, 31), and may even precede the onset of adverse reactions on ingestion, as in this girl.

Lipid transfer proteins are plant defence proteins located in the outer layers of the plants and they are especially abundant in the peels of *Rosaceae* fruits (34), with the highest levels being found in overly mature and freshly harvested fruits (35). This explains the higher clinical reactivity to the fruits when they are eaten with the peel, and the higher SPT responses to apple and peach peels in this patient (Table 4) (36). In contrast, patient 1, a profilin allergic girl not sensitized to LTPs, exhibited higher responses to fruit pulps (Table 4) which reflects their higher content in profilin (34).

The clinical presentation of peach and apple allergies in this child reflects the stability of LTPs as reactions were induced by fresh fruits as well as commercial peach juices (22, 37), and also the already described greater allergenicity of the peels of *Rosaceae* fruits (36) that is related to their higher content of LTP (34). The ingestion of peach pulp was well tolerated, but peach peel induced contact urticaria and peach commercial juices (prepared with unpeeled fruits) induced OAS and facial angioedema. The same applies for apple. The ingestion of apple with the peel (only two bites) induced OAS and a mild urticaria, whereas apple pulp (a whole fruit) was subsequently tolerated in several occasions and only once the patient noticed mild oral itching. She finally suffered a generalized urticaria after the ingestion of a peeled apple, but the association of post-prandial exercise was probably an essential cofactor to trigger the systemic reaction on that occasion.

The management of patients allergic to LTP comprises strict avoidance of fresh and processed fruits, and rescue medication that may include, in selected cases, self-injected epinephrine. Some patients allergic to the LTPs of *Rosaceae* fruits (around 1/3) may tolerate the pulp of these fruits (36), but as in this girl, reactions can be observed when exercise (or other cofactors) are associated. Therefore, as a general recommendation, patients should avoid peeled fruits. However, there are patients allergic to LTPs who exhibit a very extensive reactivity to fruits, nuts and vegetables and have to follow very restrictive elimination diets. In some of them (selected adults, mainly), peeled fruits can be allowed after assessing the tolerance in the clinic (i.e. after a negative oral challenge) and only if patients avoid cofactors, especially exercise and non-steroidal anti-inflammatory drugs (written instructions should be provided).

Apart from the *Rosaceae* fruits, LTPs have been described as allergens in other plant foods and pollens and they should be considered as

panallergens (38, 39). However, this girl only reacted to peach and apple. This is in agreement with a previous study that has shown the existence of different patterns of reactivity to LTPs (40) probably related to different epitope recognition patterns: some subjects only react to peach and apple (*Rosaceae* fruits), whereas other patients (especially those sensitized to Art v 3, the mugwort LTP) have a wider recognition pattern of foods from taxonomically unrelated families.

Lipid transfer proteins allergies are persistent, they can start early in childhood as in this girl, and patients can develop further sensitizations/reactions to cross-reactive allergens in other plant foods. For this reason a comprehensive first evaluation should be performed in all the patients, including a careful medical history to assess the tolerance to related foods, and especially to other *Rosaceae* fruits and tree nuts. SPT and IgE determinations can be performed accordingly. If sensitizations are detected – like pear in this girl – and the tolerance or reactivity is unknown, the patient should be advised to avoid it unless tolerance is assessed in the clinic.

Patients allergic to LTP may present with systemic reactions, frequently associated with OAS as in our patient, and even with isolated OAS (31). It is therefore important to have an insight in the allergens involved, especially in patients reporting OAS after the ingestion of fresh fruits (and other plant foods), because if they are sensitized to the LTPs they are at a risk of experiencing systemic reactions, whereas patients sensitized to profilin or Bet v 1 homologues are not (11). Therefore, the CRD will provide critical information for the management of these patients. CRD can be performed routinely in clinical practice. The reactivity to peels of *Rosaceae* fruits in SPTs has been used as a clinical marker of LTP sensitization (41). Recently, ALK-Abelló (Madrid, Spain) has developed two apple and one peach extracts with known contents of Mal d 1 (Bet v 1 homologue in apple), Mal d 3 and Pru p 3, respectively, and a profilin extract (from date palm pollen) that allow clinicians to perform a CRD by skin testing. Phadia (Uppsala, Sweden) has also developed immunoCaps with individual peach allergens (Pru p 1, the Bet v 1 homologue; Pru p 4 the peach profilin; and Pru p 3) to perform *in vitro* CRD.

Finally, LTP related allergies in the Spanish population are prevalent, persistent, and potentially severe, and therefore candidates for specific immunotherapy. Some preliminary data on hazelnut (42) and peach (Fernández-Rivas, unpublished results) seem promising.

Conclusion

We present two fruit allergic patients that represent two clear cut patterns of sensitization and clinical expression of food allergy: patient 1 presents a pollen-food allergy syndrome (type two food allergy) related to profilin who developed OAS with multiple fruits, and patient 2 presents a type one food allergy to LTPs from *Rosaceae* fruits who developed systemic reactions on ingestion of peach and apple. These two cases also show the improved diagnostic value of the CRD, and strengthen its utility in the routine diagnosis and management of patients. The CRD simplifies the diagnosis, and provides a new insight in the potential severity of a food allergy in relation to the capacity of the food allergens involved to induce mild or severe reactions.

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References

1. WOOD RA. The natural history of food allergy. *Pediatrics* 2003; 111: 1631–7.
2. SAMPSON HA. Update on food allergy. *J Allergy Clin Immunol* 2004; 113: 805–19.
3. PEREIRA B, VENTER C, GRUNDY J, CLAYTON B, ARSHAD SH, DEAN T. Prevalence of sensitization to food allergens, reported adverse reactions to foods, food avoidance, and food hypersensitivity among teenagers. *J Allergy Clin Immunol* 2005; 116: 884–92.
4. VENTER C, PEREIRA B, GRUNDY J, CLAYTON CB, ARSHAD SH, DEAN T. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. *Pediatr Allergy Immunol* 2006; 17: 356–63.
5. CRESPO JF, PASCUAL C, BURKS AW, HELM RM, ESTEBAN MM. Frequency of food allergy in a pediatric population from Spain. *Pediatr Allergy Immunol* 1995; 6: 39–43.
6. OSTERBALLE M, HANSEN TK, MORTZ CG, HOST A, BINDSLEV-JENSEN C. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 2005; 16: 567–73.
7. RANCÉ F, GRANDMOTTET X, GRANDJEAN H. Prevalence and main characteristics of school children diagnosed with food allergies in France. *Clin Exp Allergy* 2005; 35: 167–72.
8. ROEHR CC, EDENHARTER G, REIMANN S, et al. Food allergy and non-allergic food hypersensitivity in children and adolescents. *Clin Exp Allergy* 2004; 34: 1534–41.
9. FERNÁNDEZ RIVAS M. Alergia a los alimentos. In: SEAIC, ed. *Alergológica* 2005. Factores Epidemiológicos, Clínicos y Socioeconómicos de las Enfermedades

- Alérgicas en España en 2005. Madrid: Luzán 5 S.A. de Ediciones, 2006: 227–53.
10. 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.
 11. FERNÁNDEZ-RIVAS M, BOLHAAR S, GONZÁLEZ-MANCEBO E, et al. Apple allergy across Europe: how allergen sensitization profiles determine the clinical expression of plant food allergies. *J Allergy Clin Immunol* 2006; 118: 481–8.
 12. AALBERSE RC. Structural biology of allergens. *J Allergy Clin Immunol* 2000; 106: 228–38.
 13. BREITENEDER H, EBNER C. Molecular and biochemical classification of plant-derived food allergens. *J Allergy Clin Immunol* 2000; 106: 27–36.
 14. VAN REE R. Clinical importance of non-specific lipid transfer proteins as food allergens. *Biochem Soc Trans* 2002; 30: 910–3.
 15. AMLOT PL, KEMENY DM, ZACHARY C, PARKES P, LESSOF MH. Oral allergy syndrome (OAS): symptoms of IgE mediated hypersensitivity to foods. *Clin Allergy* 1987; 17: 33–42.
 16. ORTOLANI C, ISPANO M, PASTORELLO E, BIGI A, ANSALONI R. The oral allergy syndrome. *Ann Allergy* 1988; 61: 47–52.
 17. LESSOF MH, KELSO JM. Pollen-food allergy syndrome. *J Allergy Clin Immunol* 1996; 98: 239–40.
 18. CUESTA J, BLANCO C, FERNÁNDEZ RIVAS M, VILLALBA M. Vegetalia. *J Investig Allergol Clin Immunol* 2006; 16 (Suppl. 2): 40–4.
 19. PETERSEN AB, GUDMANN P, MILVANG-GRONAGER P, et al. Performance evaluation of a specific IgE assay developed for the ADVIA centaur immunoassay system. *Clin Biochem* 2004; 37: 882–92.
 20. VAN REE R, VOITENKO V, VAN LEEUWEN WA, AALBERSE RC. Profilin is a crossreactive allergen in pollen and vegetable foods. *Int Arch Allergy Immunol* 1992; 98: 97–104.
 21. ASERO R, MISTRELLO G, RONCAROLO D, et al. Detection of clinical markers of sensitization to profilin in patients allergic to plant-derived foods. *J Allergy Clin Immunol* 2003; 112: 427–32.
 22. SCHEURER S, LAUER I, FOETISCH K, et al. Strong allergenicity of Pru av 3, the lipid transfer protein from cherry, is related to high stability against thermal processing and digestion. *J Allergy Clin Immunol* 2004; 114: 900–7.
 23. RODRIGUEZ PEREZ R, CRESPO FJ, RODRIGUEZ J, SALCEDO G. Profilin is a relevant melon allergen susceptible to pepsin digestion in patients with oral allergy syndrome. *J Allergy Clin Immunol* 2003; 111: 634–9.
 24. 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 (1 Pt 1): 116–25.
 25. VAN REE R, FERNANDEZ-RIVAS M, CUEVAS M, VAN WIJNGAARDEN M, AALBERSE RC. Pollen-related allergy to peach and apple: an important role for profilin. *J Allergy Clin Immunol* 1995; 95: 726–34.
 26. CUESTA-HERRANZ J, LAZARO M, DE LAS HERAS M, et al. Peach allergy pattern: experience in 70 patients. *Allergy* 1998; 53: 78–82.
 27. ASERO R. Effects of birch pollen specific immunotherapy on apple allergy in birch pollen hypersensitive patients. *Clin Exp Allergy* 1998; 28: 1368–73.
 28. ASERO R. How long does the effect of birch pollen injection SIT on apple allergy last? *Allergy* 2003; 58: 435–8.
 29. 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.
 30. BOLHAAR STHP, TIEMESSEN MM, ZUIDMEER L, et al. Efficacy of birch pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and food challenges. *Clin Exp Allergy* 2004; 34: 761–9.
 31. FERNÁNDEZ-RIVAS M, GONZÁLEZ-MANCEBO E, RODRÍGUEZ PÉREZ R, et al. Clinically relevant peach allergy is related to peach lipid transfer protein, Pru p 3, in the Spanish population. *J Allergy Clin Immunol* 2003; 112: 789–95.
 32. FERNÁNDEZ RIVAS M, VAN REE R, CUEVAS M. Allergy to *Rosaceae* fruits without related pollinosis. *J Allergy Clin Immunol* 1997; 100: 728–33.
 33. DÍAZ-PERALES A, LOMBARDERO M, SÁNCHEZ-MONGE R, et al. Lipid-transfer proteins as potential plant panallergens: cross-reactivity among proteins of *Artemisia* pollen, *Castanea* nut and *Rosaceae* fruits, with different IgE-binding capacities. *Clin Exp Allergy* 2000; 30: 1403–10.
 34. MARZBAN G, PÜHRINGER H, DEY R, et al. Localisation and distribution of major apple allergens in fruit tissue. *Plant Science* 2005; 169: 1387–94.
 35. SANCHO AI, FOXALL R, RIGBY NM, et al. Maturity and storage influence on the apple (*Malus domestica*) allergen Mal d 3, a nonspecific lipid transfer protein. *J Agric Food Chem* 2006; 12: 54.
 36. FERNÁNDEZ RIVAS M, CUEVAS M. Peels of *Rosaceae* fruits have a higher allergenicity than pulps. *Clin Exp Allergy* 1999; 29: 1239–47.
 37. BRENNA O, POMPEI C, ORTOLANI C, PRAVETTONI V, FARIOLI L, PASTORELLO EA. Technological processes to decrease the allergenicity of peach juice and nectar. *J Agric Food Chem* 2000; 48: 493–7.
 38. ASERO R, MISTRELLO G, RONCAROLO D, et al. Lipid transfer protein: a pan-allergen in plant-derived foods that is highly resistant to pepsin digestion. *Int Arch Allergy Immunol* 2000; 122: 20–32.
 39. SALCEDO G, SANCHEZ-MONGE R, DIAZ-PERALES A, GARCIA-CASADO G, BARBER D. Plant non-specific lipid transfer proteins (LTPs) as food and pollen allergens. *Clin Exp Allergy* 2004; 34: 1336–41.
 40. GARCIA-SELLES FJ, DIAZ-PERALES A, SANCHEZ-MONGE R, et al. Patterns of reactivity to lipid transfer proteins of plant foods and *Artemisia* pollen: an in vivo study. *Int Arch Allergy Immunol* 2002; 128: 115–22.
 41. ASERO R. Plant food allergies: a suggested approach to allergen-resolved diagnosis in the clinical practice by identifying easily available sensitization markers. *Int Arch Allergy Immunol* 2005; 138: 1–11.
 42. ENRIQUE E, PINEDA F, MALEK T, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol* 2005; 116: 1073–9.