From Pollinosis to Digestive Allergy

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■ Abstract

Pollinosis is defined as the appearance of respiratory symptoms (rhinoconjunctivitis and/or asthma) as a result of the inhalation of pollen to which the individual is sensitized. Pollen allergy becomes all the more relevant on taking into account that it may be responsible for the development of plant food allergy, or may even constitute the direct cause of esophageal, gastric and/or intestinal inflammation in the context of a digestive allergic process. Pollen can act as a source of allergens that induce primary sensitization in the host as a result of inhalation, with secondary allergy to plant foods containing shared allergens via a cross-reactivity mechanism. The observed pattern of plant food allergy depends on the dietary habits of the population in a given geographical setting, and on the pollination found in that setting. Pollinosis may account for the greater or lesser prevalence of allergy to certain plant foods, and for the severity of the associated reactions. Beyond the digestive tract inflammation that may result from allergy to a given food, pollinosis is also intrinsically able to generate a clinically relevant or irrelevant Th2-mediated inflammatory response at digestive level, and may even give rise to eosinophilic esophagitis. Inter-relation with the airway may also extend to the digestive tract as a consequence of the systemic response that characterizes allergic disease.

Key words: Food allergy, digestive allergy, allergic asthma, eosinophilic esophagitis, pollen, pollinosis, allergic rhinoconjunctivitis.

■ Resumen

La polinosis se define como la aparición de síntomas respiratorios (rinoconjuntivitis y/o asma) secundarias a la inhalación de un polen al que el individuo está sensibilizado. La alergia al polen aún cobra más relevancia si tenemos en cuenta que puede ser la responsable de la aparición de una alergia a alimentos vegetales o, más aún, ser causante directo de una inflamación en el esófago, estómago y/o intestino conllevando a una alergia digestiva. El polen puede comportarse como una fuente de alérgenos frente a los que se produce una sensibilización primaria por vía inhalada y secundariamente aparecer la alergia a alimentos vegetales que posean alérgenos comunes por un fenómeno de reactividad cruzada. El patrón de la alergia a alimentos vegetales dependerá tanto de los hábitos dietéticos de la población de una determinada área como también de la polinización existente en ella. La polinosis puede justificar la mayor o menor prevalencia de alergia a determinados alimentos vegetales así como la gravedad de sus reacciones. Más allá de la inflamación del tubo digestivo que puede causar la alergia a un determinado alimento, la polinosis también es capaz *per se* de producir una inflamación Th2 a nivel digestivo, clínicamente relevante o irrelevante, e incluso ser la causa de una esofagitis eosinofílica. La interrelación de la vía respiratoria puede extenderse también a la digestiva como consecuencia de la respuesta sistémica que caracteriza a la enfermedad alérgica.

Palabras clave: Alergia alimentos. Alergia digestiva. Asma alérgica. Esofagitis eosinofílica. Polen. Polinosis. Rinoconjuntivitis alérgica.

Introduction

Pollinosis is defined as the appearance of respiratory symptoms (rhinoconjunctivitis and/or asthma) as a result of the inhalation of pollen to which the individual is sensitized. It is well known that allergic rhinitis and asthma are very common in the general population, the estimated prevalence being 15-25%, though the figures may vary according to patient age and geographical distribution [1]. Pollen is one of the main causes of allergic rhinitis and asthma in our setting. According to the findings of the epidemiological study, Alergológica 2005, a full 51.9% of all patients with allergic rhinitis are sensitized to some type of pollen (the latter being the most common allergen) [2], versus 43.8% of all asthmatics (pollen again being the most frequent allergen in this group). Based on these figures, it can be seen that pollinosis is an important illness in itself. However, pollen allergy becomes all the more relevant on taking into account that it may be responsible for the development of plant food allergy, or may even constitute the direct cause of esophageal, gastric and/or intestinal inflammation in the context of what may be referred to as digestive allergy. Since pollinosis is the most prevalent respiratory allergy among adults in many geographical settings, it is easy to understand that associated plant food allergy is the most common type of food allergy in adults [4]. It has been estimated that 30-60% of all pollinic patients in the European population suffer plant food allergy [5-7]. The appearance of plant food allergy in pollinic patients has been described for different types of pollen, as well as both esophageal and gastrointestinal inflammation in pollinic patients without associated food allergy. These aspects will be addressed in the present review.

Food allergy in pollinosis

In the year 2001, the European Academy of Allergy and Clinical Immunology (EAACI) Nomenclature Task Force defined food allergy as those adverse reactions to foods that are mediated immunologically, with or without the participation of IgE. Among the latter, mention may be made of cell mediated reactions [8] (Figure 1). The classification of food allergies according to the underlying immune mechanism is given in Table 1. In the present review, reference to food allergy is meant to imply IgE mediated reactions, which are the most common cause of food allergy.

Food allergy is currently an important topic in view of its high prevalence [9,10], the potential seriousness of the disease [11,12], the important associated impact upon patient, family and care giver quality of life [13,14], and the great socioeconomic burden involved [15,16].

Two types of food allergy have been described on the basis of the clinical presentation patterns of the causal allergens and the implicated physiopathological mechanisms: class 1 and class 2 food allergy [17]. In class 1 food allergy, sensitization occurs as a consequence of the allergen contained in the food within the gastrointestinal tract, and which behaves as a complete allergen, i.e., it is able to induce sensitization and an allergic response [18]. This class of food allergy is more common in children, and is one of the first manifestations of atopic disease. The causal foods contain allergens that are resistant to gastric digestion and tend to be thermostable [19]. The most important implicated foods are cow's milk, eggs and legumes. Class 2 allergy in turn is the consequence of primary sensitization due to inhaled allergens. The immune basis involves a cross-reactivity phenomenon that may be clinically relevant or irrelevant [20]. Food will induce symptoms in those patients previously sensitized to homologous allergens present in the inhaled aeroallergens. The allergen contained in food would be able to trigger an allergic reaction, but would be unable to induce sensitization. As such, it would behave as an incomplete allergen [19]. Most class 2 allergens are thermolabile and susceptible to enzymatic degradation [21]. Class 2 food allergy typically affects older children, adolescents and adults. An example would be the birch – plant
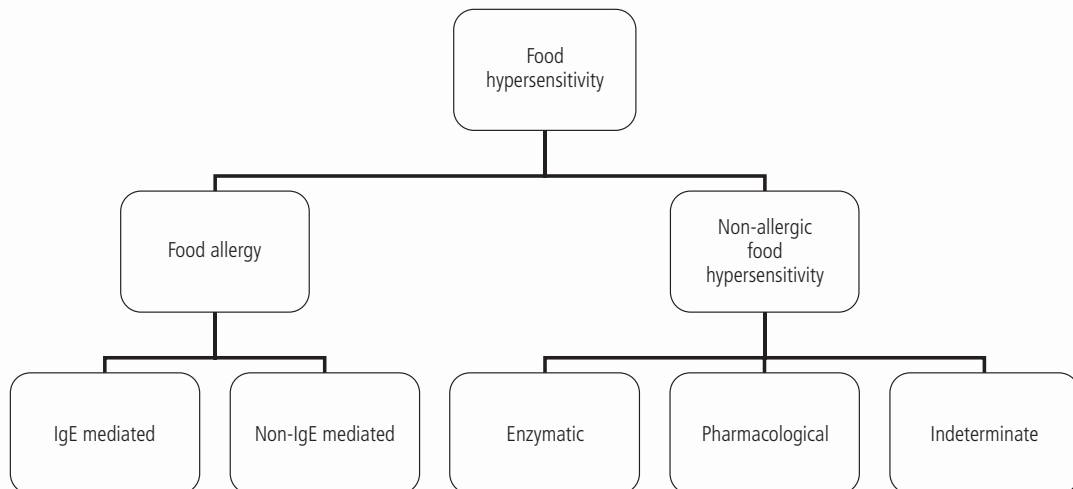

Figure. Classification of adverse reactions to foods, based on the criteria of the European Academy of Allergy and Clinical Immunology (EAACI) Nomenclature Task Force.

Table 1. Classification of food allergies according to the underlying immune mechanism

• IgE mediated
    Cutaneous
        – Urticaria
        – Angiodema

    Gastrointestinal
        – Oral allergy syndrome
        – Nausea / vomiting
        – Abdominal pain
        – Diarrhea

    Respiratory
        – Rhinoconjunctivitis
        – Asthma

    Generalized
        – Anaphylaxis

• IgE and cell mediated
    Cutaneous
        – Atopic dermatitis

    Gastrointestinal
        – Eosinophilic esophagitis
        – Eosinophilic gastroenteritis

    Respiratory
        – Asthma

• Cell mediated
    Cuaneous
        – Contact dermatitis
        – Herpetiform dermatitis

    Gastrointestinal
        – Enterocolitis
        – Proctocolitis
        – Enteropathy
        – Celiac disease

food syndrome in which sensitization to birch pollen would be responsible for the posterior development of allergy to apple, hazelnut, carrot and other plant foods that share homologous allergens [22].

Thus, pollen can act as a source of allergens that induce primary sensitization in the host as a result of inhalation, with secondary allergy to plant foods containing shared allergens through cross-reactivity with the pollen [23,24].

Pollen – food cross-reactivity

Molecular biology is very useful for understanding cross-reactivity phenomena. Since the cloning of the first pollinic allergen in 1989, corresponding to the predominant birch allergen Bet v 1 [25], there has been great progress in the molecular characterization of allergens, as reflected by the Allergome allergen database (www.allergome.org) or the official list of the International Union of Immunological Societies Nomenclature Subcommittee (www.allergen.org). Of the close to 9500 families of proteins contained in the Protein Families

Database of Alignments and Hidden Harkov Models (Pfam), "only" 29 are described as allergenic in pollen, versus 27 in plant foods. Ten families of allergens are present both in pollen and in plant foods. Of the more than 2600 families of proteins found in the seeds of plants, only the prolamine family has been described as allergenic. Four families of proteins group more than 60% of all plant food allergens: the prolamine superfamily, the cupin superfamily, the Bet v 1 homologs, and the profilins [26,27]. Of these four families, the prolamines, profilins and Bet v 1 homologs are those of particular relevance in relation to cross-reactivity between pollen and food allergens.

The prolamine superfamily

The prolamine superfamily comprises three major groups of allergens: lipid transfer proteins (LTPs), albumins 2S and the trypsin and α-amylase inhibitors. All are rich in cysteine and are stable in response to thermal processing and enzyme proteolysis [28]. Since their first description in 1999 [29,30], they have centered considerable research in view of their clinical relevance. The LTPs have been implicated in the appearance of systemic reactions, though they also may be responsible for symptoms confined to the oral cavity. These proteins have been described in many plant foods [26, 31], and are able to sensitize the host through the digestive tract [32]. There also is evidence suggesting their capacity to sensitize via the inhalatory route [33,34].

The Bet v 1 superfamily

Since the initial cloning of Bet v 1 [25], many allergens known as Bet v 1 homologs have been identified in plant foods, representing one of the most widely studied associations [22,35-38]. These allergens are thermally unstable and are vulnerable to digestion. Consequently, the associated symptoms are generally confined to the oral cavity [39].

Profilin

Profilins are found in all eukaryotic cells. There is important homology between the profilins of certain pollens and plant foods. Their first description as an allergenic source was made in 1991 by Valenta [40], and since then there have been reports of different pollen and food profilins [26,41]. These molecules are scantly resistant to gastric digestion; as a result, the symptoms can be expected to be confined to the oral cavity [42] – though systemic reactions have also been reported [43].

Pollen and plant food allergy syndrome

Having established the relationship between pollinosis and plant food allergy, it is easy to understand the pollen – plant food associations described in the literature, and which are detailed below.

Birch – plant food syndrome

In central and northern Europe, birch pollen accounts for almost 20% of overall pollen allergy. Approximately 70% of all

patients with respiratory allergy due to birch pollen also suffer plant food allergy (fundamentally rosaceous fruits, together with hazelnut, celery and carrot). The most common clinical presentation comprises local oropharyngeal manifestations when the fresh food is ingested; in comparison, the cooked food is well tolerated [39,44]. Bet v 1, a group 10 plant defense protein, is the main implicated allergen although in some cases other proteins have been described, such as Bet v 2 (profilin), Bet v 6 (isoflavone) and Bet v 8 (pectin esterase) [45,46]. Different studies have concluded that in this association, the initial triggering factor is inhalatory sensitization to birch pollen [22]. As a result, this syndrome is limited to areas characterized by important birch pollination, as in central and northern Europe.

Celery -mugwort-spice syndrome

In this association the clinical manifestations are usually systemic (urticaria, angioedema and even anaphylactic shock). The affected patients develop reactions after ingesting both raw and cooked vegetables; as a result, the causal allergens are proteins that resist gastric digestion and cooking [47,48].

Platanus – plant food (hazelnut, lettuce, apple, etc.)

Patients with respiratory allergy to *Platanus* [49,50] have been found to suffer an increased frequency of plant food allergy (hazelnut, walnut, apple, peach, lettuce, etc.), with systemic alterations as the predominant manifestation. Once of the allergens described in allergy to the pollen of *Platanus* is Pla a 3, an LTP (group 14 plant defense protein) showing partial cross-reactivity with lettuce LTP [51]. Although in this syndrome it has not been possible to confirm *Platanus* as the cause of plant food allergy, it could exert a modulating effect upon the allergic response to foods, and in some patients could even be the cause, as reported in the case of *Artemisia* pollen [34]. Additional indirect evidence of the effect of *Platanus* pollinosis in plant food allergy is the improvement of food allergy in patients subjected to *Platanus* immunotherapy versus untreated individuals [52].

Other

Artemisia-mustard, Ambrosia-melon-banana, *Parietaria*-pistachio, olive-plant foods, etc. have also been reported as associations of pollinosis and plant allergy, and are further examples of pollen-food allergies [48,53,54].

Influence of pollinosis in patterns of plant food allergy

The observed pattern of plant food allergy depends on the dietary habits of the population in a given geographical setting, and on the pollination found in that setting. Pollinosis may account for the greater or lesser prevalence of allergy to certain plant foods, and for the severity of the associated reactions. As has been commented above, in central and northern Europe

plant food allergy is often associated to birch pollinosis, and more specifically to Bet v 1. The symptoms tend to be mild and limited to the oropharyngeal cavity. However, in southern Europe and the Mediterranean, plant food allergy tends to manifest in more serious forms (systemic reactions) – LTP being one of the main implicated proteins [55,56]. In parallel, LTPs have been identified in recent years in weed and tree pollens that are responsible for important pollinosis in southern Europe and the Mediterranean. However, the precise role of pollen LTPs in relation to cross-reactivity with the LTPs of certain plant foods is not known [34,49,51,54]. It has been speculated that pollens in some cases can act as primary sensitizers, and in others as the modulators of allergic responses to plant foods – reinforcing reaction severity or expanding the diversity of plants to which the patient is allergic, according to the homology in the sequences of their LTPs [56].

However, this north-south pattern cannot be extended to all patients with allergy to pollen and plant foods, since the protein sensitization profile and clinical expression can vary greatly from one patient to another [57], particularly on taking into account that there are cofactors that can modulate the allergic response – such as physical exercise or the use of nonsteroidal antiinflammatory drugs [58,59].

Pollinosis as the cause of allergic inflammation of the digestive tract

Patients with food allergy, associated or not to pollinosis, develop more or less extensive Th2 cell mediated inflammation of the gastrointestinal tract [60,61]. There are other food allergies, such as allergic eosinophilic esophagitis or allergic eosinophilic gastroenteritis, where in some cases food allergens have been identified as the cause, and in which the type of inflammation depends on the underlying immune mechanism [62-66].

Beyond the digestive tract inflammation that may result from allergy to a given food, pollinosis is also intrinsically able to generate a clinically relevant or irrelevant Th2-mediated inflammatory response at digestive level, and may even give rise to eosinophilic esophagitis.

Impact of pollinosis upon intestinal inflammation

Since pollen can reach the digestive tract as a result of swallowing [67], and considering that the gastrointestinal system is shock organ, patients with pollinosis may also experience symptomatic or asymptomatic allergic inflammation at esophageal or even gastrointestinal level. However, on taking into account that the enzyme degradation inherent to the digestive process denaturalizes most pollen allergens [68], it would be difficult to explain the connection between pollinosis and digestive tube inflammation as a shock organ effect alone.

There is a large volume of scientific documentation on the concept of single airway integrity in which an important connection is demonstrated between the upper and the lower respiratory airways [1]. Such an inter-relationship is fundamentally explained by the fact that allergic inflammation is the result of a

systemic reaction [69]. If we accept the concept of "one airway, one disease", it may be thought that the systemic Th2 mediated allergic responses involve the mediation of a series of cytokines and chemokines that can affect the mucosal membranes of different organs or systems that share common structures and components – such as the respiratory and digestive apparatuses.

Few data are available on this aspect, however. In patients with birch pollen allergy, it has been demonstrated that provocation with Bet v 1 via colonoscopy is able to induce intestinal inflammation [70]. Magnusson et al. [71] have concluded that in patients with birch pollinosis and birch – plant food syndrome, a duodenal biopsy obtained during the pollination season shows greater infiltration on the part of eosinophils and mast cells than in biopsies taken outside the pollination season. In both seasons the patients avoided the consumption of foods implicated in the birch – plant food syndrome. In addition, most of these patients reported nonspecific gastrointestinal discomfort during the pollination season. Onbasi et al. [72] have demonstrated the increased presence of eosinophils in the esophagus of patients with allergy to the pollen of gramineous species versus the control population – though this infiltration was not correlated to clinical digestive symptoms.

On analyzing this inter-relationship between the respiratory and digestive systems in the opposite sense, i.e., based on patients with food allergy but no associated pollinosis, the existing literature is likewise seen to be scarce. Wallaert et al. [73] reported that the induced sputum of patients with food allergy but no rhinitis or asthma contains an increased concentration of eosinophils, neutrophils and IL-8 compared with the control population. Thaminy et al. in turn reported that patients with food allergy but no respiratory allergy exhibit greater asymptomatic bronchial hyper-responsiveness than the population without food allergy [74].

Thus, evidence exists that pollinosis can induce Th2 mediated inflammation of the digestive tract as the expression of a systemic allergic response.

Pollinosis in eosinophilic esophagitis

Eosinophilic esophagitis is a disorder characterized by the presence of a dense eosinophilic infiltrate with squamous epithelial hyperplasia, in the absence of gastric or intestinal mucosal anomalies. The first description was published in 1977 [75], though a hallmark was reached in 1995, when eosinophilic esophagitis was established as a disorder that could be related to food allergy [76]. The diagnostic criteria according to the latest consensus document of the American Society of Pediatric Gastroenterology and the American Gastroenterological Association Institute are found in Table 2 [77].

An allergic etiology based on an IgE, cellular or mixed mechanism appears to be the cause, as reflected by the existing evidence: 1) Between 60-80% of all patients with eosinophilic esophagitis suffer atopic dermatitis and/or allergic rhinitis – asthma and/or food allergy [62,78]. 2) Many patients improve with diets from which the possible food allergens have been excluded (exclusion diets) [76,77]. 3) Diets excluding foods to which the patients are allergic, as determined by skin tests (prick and patch tests), have been shown to be effective in some patients [79]. 4) The inflammation profile corresponds to a predominantly Th2 mediated pattern [80,81]. 5) Allergy to a pollen can induce eosinophilic inflammation at esophageal level [72,82,83]. This point is further commented below.

In the year 2001, Mishra et al. published a study involving a model of mice allergic to *Aspergillus*, where after intranasal provocation with the aeroallergen, an eosinophilic inflammatory response was observed at bronchial level, together with peripheral blood eosinophilia and – most importantly – eosinophilic inflammation at esophageal level [83]. These results coincide with the observations of Onbasi et al. mentioned above.

The only literature source referring to pollinosis as the cause of eosinophilic esophagitis in humans is the clinical case published by Fogg, who described a patient with criteria of eosinophilic esophagitis without associated food allergy, and with seasonal pollinic allergic rhinitis and asthma. After following-up on the patient during three pollination seasons, including the obtainment of esophageal biopsies within and outside the mentioned seasons, the author concluded that eosinophilic esophagitis only appeared during the pollination season – thus establishing pollinosis as the underlying cause [82].

Taking into account the increase in diagnosed cases of eosinophilic esophagitis in the last two decades [78,84,85], associated in most cases to atopy, and based on the evidence that in some cases allergic responses are the cause, with the implication also of pollen, it can be concluded that pollinosis always should be evaluated in these patients.

In conclusion, it can be affirmed that pollinosis is not limited to rhinoconjunctivitis and/or bronchial asthma, but can also be responsible for the posterior development of plant food allergy, or may intrinsically induce digestive tract inflammation (clinically relevant or otherwise). Inter-relation with the airway may also extend to the digestive tract as a consequence of the systemic response that characterizes allergic disease.

Table 2. Diagnostic guidelines for eosinophilic esophagitis of the American Society of Pediatric Gastroenterology and the American Gastroenterological Association Institute

– Clinical manifestations compatible with wsophagitis or esophageal dysfunction

– ≥ 15 eosinophils per high magnification field

– Lack of response to high-dose proton pump inhibitor therapy (up to 2 mg/kg/day) or pHmetry within the normal range

References

1. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group; World Health Organization. Allergic Rhinitis and Its Impact on asthma. J Allergy Clin Immunol 2001; 108: S147-334.

2. Navarro A. Rinitis. En: SEAIC & Schering-Plough editores. Factores epidemiológicos, clínicos y socioeconómicos de las enfermedades alérgicas en España en 2005. Madrid: Luzán 5, S.A. Ediciones; 2006. p.107-131.

3. Quirce S. Asma. En: SEAIC & Schering-Plough editores. Factores epidemiológicos, clínicos y socioeconómicos de las enfermedades alérgicas en España en 2005. Madrid: Luzán 5, S.A. Ediciones; 2006. p.133-158.

4. Fernandez-Rivas M. Alergia a los alimentos. En: SEAIC & Schering-Plough editores. Factores epidemiológicos, clínicos y socioeconómicos de las enfermedades alérgicas en España en 2005. Madrid: Luzán 5, S.A. Ediciones; 2006. p.227-253.

5. Bircher AJ, Van Melle G, Haller E, Curty B, Frei PC. 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.

6. Osterballe M, Hansen TK, Mortz CG, Høst 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. Ghunaim N, Grönlund H, Kronqvist M, Grönneberg R, Söderström L, Ahlstedt S, van Hage-Hamsten M. Antibody profiles and self-reported symptoms to pollen-related food allergens in grass pollen-allergic patients from northern Europe. Allergy. 2005; 60:185-91.

8. Johansson SGO, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Átela T, et al. A revised nomenclature for allergy: an position statement from the EAACI task force. Allergy 2001; 56: 813-824.

9. Zuidmeer L, Goldhahn K, Rona RJ, Gislason D, Madsen C, Summers C, Sodergren E, Dahlstrom J, Lindner T, Sigurdardottir ST, McBride D, Keil T. The prevalence of plant food allergies: a systematic review. J Allergy Clin Immunol. 2008; 121:1210-1218

10. Cruz NV, Wilson BG, Fiocchi A, Bahna SL; American College of Allergy, Asthma and Immunology Adverse Reactions to Food Committee.Survey of physicians' approach to food allergy, Part 1: Prevalence and manifestations. Ann Allergy Asthma Immunol. 2007; 99:325-33.

11. Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006.J Allergy Clin Immunol. 2007; 119:1018-9.

12. Simons FE. Anaphylaxis. J Allergy Clin Immunol. 2008 ; 121: S402-7.

13. Ostblom E, Egmar AC, Gardulf A, Lilja G, Wickman M. The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. Allergy. 2008; 63:211-8.

14. Marklund B, Ahlstedt S, Nordström G. Food hypersensitivity and quality of life. Curr Opin Allergy Clin Immunol. 2007; 7:279-87.

15. Flabbee J, Petit N, Jay N, Guénard L, Codreanu F, Mazeyrat R, Kanny G, Moneret-Vautrin DA. The economic costs of severe anaphylaxis in France: an inquiry carried out by the Allergy Vigilance Network. Allergy. 2008; 63:360-5.

16. Mills EN, Mackie AR, Burney P, Beyer K, Frewer L, Madsen C, Botjes E, Crevel RW, van Ree R. The prevalence, cost and basis of food allergy across Europe.Allergy. 2007; 62:717-22.

17. Breiteneder H, Ebner C. Molecular and biochemical classification of plant-derived food allergens. J Allergy Clin Immunol. 2000; 106:27-36.

18. Aalberse RC. Structural biology of allergens. J Allergy Clin Immunol. 2000; 106:228-38.

19. Astwood JD, Leach JN, Fuchs RL. Stability of food allergens to digestion in vitro. Nat Biotech 1996; 14: 1269-1273.

20. Ebner C, Birkner T, Valenta R, Rumpold H, Breitenbach M, Scheiner O, Kraft D. Common epitopes of birch pollen and apples--studies by western and northern blot. J Allergy Clin Immunol. 1991; 88:588-94.

21. Sampson HA. Update on food allergy. J Allergy Clin Immunol. 2004; 113: 805-19.

22. Vieths S, Scheurer S, Ballmer-Weber B. Current understanding of cross-reactivity of food allergens and pollen. Ann NY Acad Sci 2002; 964: 47-68.

23. Kazemi-Shirazi L, Pauli G, Purohit A, Spitzauer S, Fröschl R, Hoffmann-Sommergruber K, Breiteneder H, Scheiner O, Kraft D, Valenta R. 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.

24. 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.

25. Breiteneder H, Pettenburger K, Bito A, Valenta R, Kraft D, Rumpold H, Scheiner O, Breitenbach M. The gene coding for the major birch pollen allergen Betv1, is highly homologous to a pea disease resistance response gene. EMBO J. 1989; 8:1935-8.

26. Radauer C, Breiteneder H. Evolutionary biology of plant food allergens. J Allergy Clin Immunol. 2007; 120:518-25.

27. Radauer C, Bublin M, Wagner S, Mari A, Breiteneder H.Allergens are distributed into few protein families and possess a restricted number of biochemical functions. J Allergy Clin Immunol. 2008; 121:847-52.

28. Breiteneder H, Mills EN. Molecular properties of food allergens. J Allergy Clin Immunol. 2005; 115:14-23.

29. Sánchez-Monge R, Lombardero M, García-Sellés FJ, Barber D, Salcedo G. Lipid-transfer proteins are relevant allergens in fruit allergy. J Allergy Clin Immunol. 1999; 103:514-9.

30. Pastorello EA, Farioli L, Pravettoni V, Ortolani C, Ispano M, Monza M, Baroglio C, Scibola E, Ansaloni R, Incorvaia C, Conti A. The major allergen of peach (Prunus persica) is a lipid transfer protein. J Allergy Clin Immunol. 1999; 103:520-6.

31. Ahrazem O, Ibanez MD, Lopez-Torrejon G, Sanchez-Monge R, Sastre J, Lombardero M, Barber D, Salcedo G. Lipid Transfer Proteins and Allergy to Oranges. Int Arch Allergy Immunol. 2005; 137:201-210.

32. van Ree R. Clinical importance of non-specific lipid transfer proteins as food allergens. Biochem Soc Trans. 2002; 30:910-3.

33. Palacin A, Quirce S, Armentia A, Fernández-Nieto M, Pacios LF, Asensio T, Sastre J, Diaz-Perales A, Salcedo G. Wheat lipid transfer protein is a major allergen associated with baker's asthma. J Allergy Clin Immunol. 2007; 120:1132-8.

34. Lombardero M, García-Sellés FJ, Polo F, Jimeno L, Chamorro MJ, García-Casado G, Sánchez-Monge R, Díaz-Perales A, Salcedo G, Barber D. 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.

35. Mittag D, Vieths S, Vogel L, Wagner-Loew D, Starke A, Hunziker P, Becker WM, Ballmer-Weber BK. Birch pollen-related food allergy to legumes: identification and characterization of the Bet v 1 homologue in mungbean (Vigna radiata), Vig r 1. Clin Exp Allergy. 2005; 35:1049-55.

36. Mittag D, Akkerdaas J, Ballmer-Weber BK, Vogel L, Wensing M, Becker WM, Koppelman SJ, Knulst AC, Helbling A, Hefle SL, Van Ree R, Vieths S. Ara h 8, a Bet v 1-homologous allergen

from peanut, is a major allergen in patients with combined birch pollen and peanut allergy. J Allergy Clin Immunol. 2004; 114:1410-7.

37. Breiteneder H, Radauer C. A classification of plant food allergens. J Allergy Clin Immunol. 2004; 113:821-30.

38. Ebner C, Hirschwehr R, Bauer L, Breiteneder H, Valenta R, Ebner H, Kraft D, Scheiner O. Identification of allergens in fruits and vegetables: IgE cross-reactivities with the important birch pollen allergens Bet v 1 and Bet v 2 (birch profilin). J Allergy Clin Immunol. 1995; 95:962-9.

39. Breitender H, Mills E. Plant food allergens – structural and functional aspects of allergenicity . Biotech adv 2005; 23: 395-399.

40. Valenta R, Duchêne M, Pettenburger K, Sillaber C, Valent P, Bettelheim P, Breitenbach M, Rumpold H, Kraft D, Scheiner O. Identification of profilin as a novel pollen allergen; IgE autoreactivity in sensitized individuals. Science. 1991 2; 253:557-60.

41. Lopez-Torrejon G, Ibanez MD, Ahrazem O, Sanchez-Monge R, Sastre J, Lombardero M, Barber D, Salcedo G. Isolation, cloning and allergenic reactivity of natural profilin Cit s 2, a major orange allergen. Allergy. 2005;60:1424-9.

42. Asero R, Mistrello G, Roncarolo D, Amato S, Zanoni D, Barocci F, Caldironi G. Detection of clinical markers of sensitization to profilin in patients allergic to plant-derived foods. J Allergy Clin Immunol. 2003; 112:427-32.

43. Fäh J, Wüthrich B, Vieths S. Anaphylactic reaction to lychee fruit: evidence for sensitization to profilin. Clin Exp Allergy. 1995; 25:1018-2.

44. Eriksson NE, Formgren H, Svenonius E. Food hypersensitivity in patients with pollen allergy. Allergy. 1982; 37:437-43.

45. Karamloo F, Wangorsch A, Kasahara H, Davin LB, Haustein D, Lewis NG, Vieths S. Phenylcoumaran benzylic ether and isoflavonoid reductases are a new class of cross-reactive allergens in birch pollen, fruits and vegetables. Eur J Biochem. 2001; 268:5310-20.

46. Mahler V, Fischer S, Heiss S, Duchêne M, Kraft D, Valenta R. cDna cloning and characterization of a cross-reactive birch pollen allergen: identification as a pectin esterase. Int Arch Allergy Immunol. 2001; 124:64-6.

47. Wüthrich B, Dietschi The celery-carrot-mugwort-condiment syndrome: skin test and RAST results. Schweiz Med Wochenschr. 1985; 115:258-64.

48. Egger M, Mutschlechner S, Wopfner N, Gadermaier G, Briza P, Ferreira F. Pollen-food syndromes associated with weed pollinosis: an update from the molecular point of view. Allergy. 2006; 61:461-76.

49. Enrique E, Cisteró-Bahíma A, Bartolomé B, Alonso R, San Miguel-Moncín MM, Bartra J, Martínez A. Platanus acerifolia pollinosis and food allergy. Allergy. 2002 57:351-6.

50. Miralles JC, Caravaca F, Guillén F, Lombardero M, Negro JM.Cross-reactivity between Platanus pollen and vegetables. Allergy. 2002; 57:146-9.

51. San Miguel-Moncín M, Krail M, Scheurer S, Enrique E, Alonso R, Conti A, Cisteró-Bahíma A, Vieths S. Lettuce anaphylaxis: identification of a lipid transfer protein as the major allergen. Allergy. 2003; 58:511-7.

52. Alonso R, Enrique E, Pineda F, Basagaña M, San Miguel-Moncín MM, Bartra J, Palacios R, Cisteró-Bahíma A. An observational study on outgrowing food allergy during non-birch pollen-specific, subcutaneous immunotherapy. Int Arch Allergy Immunol. 2007; 143:185-9.

53. Figueroa J, Blanco C, Dumpiérrez AG, Almeida L, Ortega N, Castillo R, Navarro L, Pérez E, Gallego MD, Carrillo T. Mustard allergy confirmed by double-blind placebo-controlled food challenges: clinical features and cross-reactivity with mugwort pollen and plant-derived foods. Allergy. 2005; 60:48-5.

54. Florido Lopez JF, Quiralte Enriquez J, Arias de Saavedra Alías JM, Saenz de San Pedro B, Martin Casañez E. An allergen from Olea europaea pollen (Ole e 7) is associated with plant-derived food anaphylaxis. Allergy. 2002; 57 71:53-9.

55. Fernández-Rivas M, Bolhaar S, González-Mancebo E, Asero R, van Leeuwen A, Bohle B, Ma Y, Ebner C, Rigby N, Sancho AI, Miles S, Zuidmeer L, Knulst A, Breiteneder H, Mills C, Hoffmann-Sommergruber K, van Ree R. 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.

56. Zuidmeer L, van Ree R. Lipid transfer protein allergy: primary food allergy or pollen/food syndrome in some cases. Curr Opin Allergy Clin Immunol. 2007 7:269-73.

57. Aleman A, Sastre J, Quirce S, de la Heras M, Carnes J, Fernandez-Caldas E, Pastor C, Blazquez AB, Vivanco F, Cuesta Herranz, J. Allergy to kiwi: A double blind, placebo-controlled, food challenge study in patients from a birch-free area. J Allergy Clinical Immunol 2004; 113:543-50.

58. Fujii H, Kambe N, Fujisawa A, Kohno K, Morita E, Miyachi Y. Food-dependent exercise-induced anaphylaxis induced by low dose aspirin therapy.Allergol Int. 2008; 57:97-8.

59. Pastorello EA, Farioli L, Conti A, Pravettoni V, Bonomi S, Iametti S, Fortunato D, Scibilia J, Bindslev-Jensen C, Ballmer-Weber B, Robino AM, Ortolani C.Wheat IgE-mediated food allergy in European patients: alpha-amylase inhibitors, lipid transfer proteins and low-molecular-weight glutenins. Allergenic molecules recognized by double-blind, placebo-controlled food challenge.Int Arch Allergy Immunol. 2007;144:10-22.

60. Knutson TW, Bengtsson U, Dannaeus A, Ahlstedt S, Stålenheim G, Hällgren R, Knutson L. Intestinal reactivity in allergic and nonallergic patients: an approach to determine the complexity of the mucosal reaction. J Allergy Clin Immunol. 1993 91:553-9.

61. Bengtsson U, Rognum TP, Brandtzaeg P, Kilander A, Hansson G, Ahlstedt S, Hanson LA. IgE-positive duodenal mast cells in patients with food-related diarrhea. : Int Arch Allergy Appl Immunol. 1991; 95:86-91.

62. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. J Allergy Clin Immunol. 2002; 109:363-8.

63. Rothenberg ME.Eosinophilic gastrointestinal disorders (EGID). J Allergy Clin Immunol. 2004 113:11-28.

64. Sampson HA. Food allergy. Part 1: immunopathogenesis and clinical disorders. J Allergy Clin Immunol. 1999; 103:717-28.

65. Bischoff SC. Mucosal allergy: role of mast cells and eosinophil granulocytes in the gut. Baillieres Clin Gastroenterol. 1996; 10:443-59.

66. Tella R, Gaig P, Lombardero M, García-Ortega P, Bartra J, Papo M, Batlle X. Allergic eosinophilic gastroenteritis in a child with Crohn's disease. J Investig Allergol Clin Immunol. 2004; 14:159-61.

67. Wilson AF, Novey HS, Berke RA, Surprenant EL. Deposition of inhaled pollen and pollen extract in human airways. N Engl J Med. 1973; 288:1056-8.

68. Einarsson R, Renck B, Taudorf E. In vitro studies of degradation

of birch and timothy pollen allergen preparations by human duodenal juice. Allergy. 1988; 43:469-72.

69. Togias AG. Systemic immunologic and inflammatory aspects of allergic rhinitis Allergy Clin Immunol. 2000; 106:S247-50.

70. Mayer JH, Gastell S, Pickert C, Bischoff SC. Recombinant Bet v 1, the major birch pollen allergen, induces wheal and flare reaction in gut mucosa of selected patients. Abstract presented at the XXth Congress of the EAACI , May 9-13, 2001, Berlin, Germany.

71. Magnusson J, Lin XP, Dahlman-Höglund A, Hanson L LA, Telemo E, Magnusson O, Bengtsson U, Ahlstedt S.Seasonal intestinal inflammation in patients with birch pollen allergy. J Allergy Clin Immunol. 2003; 112:45-50.

72. Onbasi K, Sin AZ, Doganavsargil B, Onder GF, Bor S, Sebik F. Eosinophil infiltration of the oesophageal mucosa in patients with pollen allergy during the season. Clin Exp Allergy. 2005; 35:1423-31.

73. Wallaert B, Gosset P, Lamblin C, Garcia G, Perez T, Tonnel AB. Airway neutrophil inflammation in nonasthmatic patients with food allergy. Allergy. 2002 ; 57:405-10

74. Thaminy A, Lamblin C, Perez T, Bergoin C, Tonnel AB, Wallaert B, Increased frequency of asymptomatic bronchial hyperresponsiveness in nonasthmatic patients with food allergy. Eur Respir J. 2000; 16:1091-4.

75. Dobbins JW, Sheahan DG, Behar J. Eosinophilic gastroenteritis with esophageal involvement. Gastroenterology. 1977; 72:1312-6.

76. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology. 1995; 109:1503-12.

77. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME; First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology. 2007; 133: 1342-63.

78. Liacouras CA, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeao E, Flick J, Kelly J, Brown-Whitehorn T, Mamula P, Markowitz JE. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol. 2005; 3:1198-206.

79. Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA.Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. Ann Allergy Asthma Immunol. 2005; 95:336-43.

80. Remedios M, Campbell C, Jones DM, Kerlin P.. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. Gastrointest Endosc. 2006; 63:3-12.

81. Gupta SK, Fitzgerald JF, Kondratyuk T, HogenEsch H. Cytokine expression in normal and inflamed esophageal mucosa: a study into the pathogenesis of allergic eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2006; 42:22-6.

82. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. J Allergy Clin Immunol. 2003;112:796-7.

83. 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.

84. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. N Engl J Med. 2004 ;351:940-1.

85. Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic esophagitis in Western Australia. Arch Dis Child. 2006; 91:1000-4.

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