

# Latex–Fruit Syndrome

*Carlos Blanco, MD, PhD*

## Address

Servicio de Alergia, Hospital Universitario Dr. Negrín, c/Barrenco de la Ballena s/n, 35012 Las Palmas de Gran Canaria, Spain.

E-mail: cblague@gobiernodecanarias.org

**Current Allergy and Asthma Reports** 2003, 3:47–53

Current Science Inc. ISSN 1529-7322

Copyright © 2003 by Current Science Inc.

Natural rubber latex immunoglobulin E-mediated hypersensitivity is probably one of the most relevant challenges that has been faced in the treatment of allergies during recent years. Additionally, allergen cross-reactivity has arisen as another very important problem, in the difficulty in diagnosing it and in its clinical implications. It is clear that some latex allergens cross-react with plant-derived food allergens, the so-called latex–fruit syndrome, with evident clinical consequences. Although the foods most frequently involved are banana, avocado, kiwi, and chestnut, several others are also implicated. Investigations point to a group of defense-related plant proteins, class I chitinases, which cross-react with a major latex allergen, hevein, as the panallergens responsible for the syndrome. This review focuses on our current understanding of the latex–fruit syndrome.

## Introduction

Natural rubber latex (NRL) immunoglobulin E (IgE)-mediated hypersensitivity has been recognized as a very important international health problem during recent years [1,2•]. The increase in frequency of NRL allergy, the potential severity of its induced reactions, and its presentation as an occupational disease in workers using gloves are matters of great concern. It has been demonstrated that NRL can act not only as a contact allergen but also as an aeroallergen. Scientific efforts have resulted in the identification of several NRL antigens, 12 of which have received an international nomenclature designation (Table 1) [3]. Among them, prohevein, or Hev b 6.01, is a chitin-binding protein with a molecular weight (MW) of approximately 20 kDa, which seems to be a major NRL allergen. The IgE-binding capacity of prohevein is mostly attributed to its N-terminal domain, known as hevein or Hev b 6.02, with a MW of only 4.7 kDa [4].

It is now well known that certain IgE-mediated sensitizations to aeroallergens are significantly associated with a variety of food hypersensitivities. These associated allergies, which are very important from the clinical point of view, are sometimes referred to as “syndromes.”

An example is the pollen-food allergy syndrome, which includes several associations, such as birch pollen with rosaceae fruits, ragweed with melons, and mugwort with celery [5]. The immunopathologic basis for these clinical associations is the cross-reactivity among antigens from different sources, owing to molecular similarities among their epitopes [6]. However, in vitro cross-reactions sometimes have no clinical implications, except confusing diagnosis with false-positive results of tests for specific IgE.

Some of the antigens responsible for the clinically significant cross-reactivities between aeroallergens and foods have been already identified [7••]. In fact, the characterization of the major birch-pollen allergen Bet v 1 and its homologues has played a critical role in the understanding of the pollen-food allergy syndrome. Birch-pollen allergens constitute a ubiquitous family of plant defense-related proteins, belonging to one of the groups of the so-called pathogenesis-related proteins (PRP). These PRP can increase their expression in response to certain external factors, leading to the hypothesis that modern chemically treated plants could be more allergenic than they were some years ago [8•]. Another group of PRP recently identified as fruit allergens are lipid transfer proteins (LTP) [9]. In a similar way, profilins are a group of allergenic proteins associated with the cytoskeleton system, very commonly found in the plant kingdom, which, therefore, can act as panallergens [10].

It is very interesting that although in infants and young children food allergy usually precedes aeroallergen hypersensitivity (primary sensitization to ingested antigens), the opposite is frequently observed in adults. This fact suggests that in adults, most food allergies can be the result of a primary sensitization to inhalant antigens, which sometimes cross-react with food allergens, with or without clinical consequences [6,7••].

## Latex–Fruit Syndrome

In the early 1990s, a patient with NRL and banana-associated allergy was first reported [11]. Although there is no botanical relationship between both species, cross-reactivity was demonstrated through radioallergosorbent test (RAST)-inhibition assays. Soon after, some other patients allergic to both NRL and certain plant foods were described [12,13]. In 1993, there were some reports on patients with latex–chestnut hypersensitivity, and cross-reaction was also demonstrated between them [14–16].

**Table 1. Latex allergens and their potential cross-reactivities**

| Allergen | Identification         | KDa      | Allergenecity | Cross-reactivity or homologues                                                          |
|----------|------------------------|----------|---------------|-----------------------------------------------------------------------------------------|
| Hev b 1  | REF                    | 14.6, 58 | Major in SB   | Papain                                                                                  |
| Hev b 2  | $\beta$ 1-3-glucanase  | 34–36    | Minor         | Other glucanases                                                                        |
| Hev b 3  | REF homologue          | 24–27    | Major in SB   | —                                                                                       |
| Hev b 4  | Microhelix protein     | 50–57    | Minor         | —                                                                                       |
| Hev b 5  | Acidic protein         | 16       | Major         | Kiwi acidic protein                                                                     |
| Hev b 6  | Prohevein/hevein       | 20/4.7   | Major         | CBP 20 and PRP 4A (tobacco)<br>Win 1, Win 2 ( <i>Solanaceae</i> )<br>Class I chitinases |
| Hev b 7  | Patatin homologue      | 43       | Minor         | Patatin ( <i>Solanaceae</i> )                                                           |
| Hev b 8  | Profilin               | 14       | Minor         | Pollen-food panallergen                                                                 |
| Hev b 9  | Enolase                | 51       | Minor         | Mold enolases                                                                           |
| Hev b 10 | SO-dismutase           | 26       | Minor         | Mold SO-dismutases                                                                      |
| Hev b 11 | Class I chitinase      | 33       | Minor         | Class I chitinases                                                                      |
| Hev b 12 | Lipid transfer protein | 9        | Minor         | Food-lipid transfer proteins                                                            |
| —        | Hevamine               |          | Minor         | Lysozyme                                                                                |

CBP—chitin-binding protein; PRP—pathogenesis-related proteins; REF—rubber elongation factor; SB—spina bifida patients; SO—superoxide; Win—wound-induced.

In 1994, the existence of a latex–fruit syndrome was proposed, base on the clinical observation of an unexpected but significant high rate of immediate fruit hypersensitivity on a group of 25 patients with NRL allergy [17]. In this study, almost 50% of patients with NRL allergy showed food allergy. Implicated fruits were mainly chestnut, avocado, and banana, although kiwi, papaya, and other foods were also involved. With respect to their clinical manifestations, 50% of the adverse reactions were systemic anaphylaxis, thus indicating the clinical relevance of these associated sensitizations, and the other 50% varied among urticaria, angioedema, and oral allergy syndrome.

Foods responsible for the adverse reactions in a group of 80, mainly adult, patients with NRL allergy who were attended in our outpatient clinic, as well as their clinical manifestations, are summarized in Figure 1. Approximately 45% of them (36 out of 80) showed at least one clinically relevant food-associated allergy. Among them, a total of 110 food symptomatic sensitizations were diagnosed. Banana and avocado hypersensitivities were the most frequent ones (24% of the 80 patients with NRL allergy showed reaction to each of them), followed by chestnut (22%), and kiwi (20%). Sixteen of these patients with NRL allergy (20%) showed simultaneous allergy to three or more foods, and in almost 50% of them, the number of food sensitivities increased with time. By clinical history, NRL allergy precedes food hypersensitivity in 21 patients, a simultaneous food and latex allergy onset occurred in eight cases, and food allergy was present before NRL allergy in the remaining seven patients.

Although there is no direct taxonomic relationship among the various vegetal species involved in this latex–fruit syndrome, its existence has been fully confirmed by other authors from different countries. In a Finnish study, 52% of 31 patients with NRL allergy reported symptoms

after eating bananas, and banana prick by prick test (PPT) showed positive results in 35% of them [18]. Among a series of 17 patients with NRL allergy, a 58% rate of associated fruit allergy to banana or avocado was found [19]. Other authors described that 50% of 16 patients with NRL allergy reported symptoms after eating bananas, and banana PPT was positive in 36% of 14 patients [20]. Among 47 patients with NRL allergy from Canada, 36% manifested a clinical allergy to at least one food, with banana, potato, and avocado the most frequently implicated [21]. Statistical comparisons with a control group demonstrated significant associated sensitizations among NRL and several foods, including avocado, potato, banana, tomato, chestnut, and kiwi.

In a larger series of patients with NRL allergy, 42.6% of 136 patients reported adverse reactions after ingestion of a wide range of fruits, with kiwi and banana the most frequently reported [22]. Cross-reacting IgE antibodies recognizing NRL and fruit allergens (avocado, banana, chestnut, kiwi, papaya, passion fruit, fig, melon, mango, pineapple, peach, and tomato) were demonstrated by RAST-inhibition tests. More recently, 49 potential allergic reactions to foods were identified in 29 (21%) of 137 patients from the United States [23]. Foods responsible for these reactions included not only banana, avocado, and kiwi, but also shellfish and fish.

A comparison among these studies and our series of patients lead to the following observations.

#### **Rate of food hypersensitivity among patients with latex allergy**

The rate of patients with NRL allergy who show associated food allergy varies from 21% [23] to 58% [19] among the studies considered (Table 2). This could be explained by differences in diagnostic criteria, both for NRL and for

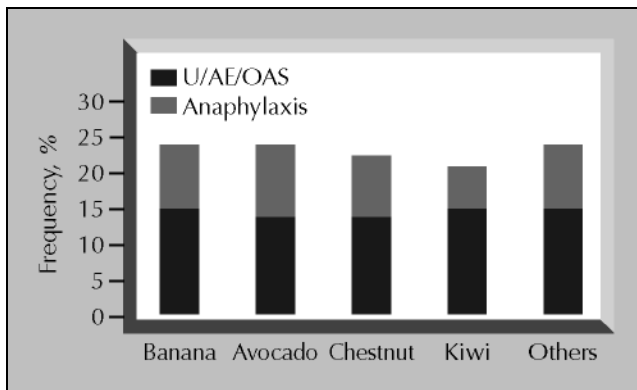


**Figure 1.** Relative frequency and clinical manifestations of associated food allergies in a group of patients who were allergic to latex. Other foods included are papaya, fig, passion fruit, *Prunoideae* fruits (peach, medlar, plum), potato, nuts, fish, and cereals. AE—angioedema; OAS—oral allergy syndrome; U—urticaria.

food allergies. In this context, criteria for diagnosing NRL allergy are not standardized, a gold standard is not available, and, therefore, patients with NRL allergy are not similarly selected. Furthermore, food oral challenge tests have not been performed in these patients, leading to a possible overdiagnosis of food allergies among them. However, differences in food consumption habits could also play a role (discussed later). However, as usually observed when dealing with food allergy, the rate of food sensitization among patients with NRL allergy could be considerably higher than reported, because many of these patients are nonsymptomatic [21].

#### Food hypersensitivities associated to latex allergy

As previously suspected [17], the type and proportion of food sensitivities associated with NRL allergy vary among studies. This fact may be explained by differences in the nutritional habits among countries [22]. For example, chestnut and avocado allergies are less frequently diagnosed in Germany than in Spain, probably because these foods are less commonly consumed among the German population. However, in this context, the high rate of potato or tomato allergies found in Canada [21] or of shellfish allergy described in the United States is remarkable [23]. Table 3 summarizes some of the food hypersensitivities associated with NRL allergy.

#### Severity of food-induced adverse reactions

In the same way, the rate of food anaphylactic reactions vary among the studies mentioned, from 50% [17]–42% in our series of 80 patients—to less than 5% [22] of recorded food adverse reactions. Again, differences in diagnostic criteria and food consumption habits could explain these figures. Actually, certain foods seem to be more prone to induce severe reactions—for example, fig, papaya, and tomato. Meanwhile, foods such as potato usually induce mild local reactions [21]. As commonly described

with NRL allergy, a systemic anaphylaxis could be the initial manifestation of the food hypersensitivity.

#### Other clinical features of the latex–fruit syndrome

Although NRL allergy precedes food hypersensitivity in most patients, the opposite is also seen in some subjects, as mentioned earlier. In agreement with our results, other authors found that the onset of NRL allergy precedes food allergy in 12 out of 29 patients; however, in 11 cases, food allergy was present before, and one patient reported a simultaneous onset [23]. As we have observed in 50% of our patients, other studies have shown that in many cases the spectrum of food allergies may increase with time. For example, in a series of 29 patients, five developed new food hypersensitivities after acquiring NRL allergy [23]. The question is whether this fact reflects new allergies or just cross-reactions.

#### Latex sensitization among patients with food allergies

Among a group of 17 patients allergic to avocado, 10 showed associated IgE-mediated hypersensitivity to NRL [24]. In an epidemiologic survey on greenhouse workers, it was demonstrated that certain food sensitizations—avocado, chestnut, banana, and almond—increased as much as 24 times the risk for NRL allergy [25]. Other studies have investigated the prevalence of NRL hypersensitivity among patients diagnosed with fruit allergy. In one of them, six out of 57 patients with fruit allergies were found to suffer from clinically relevant NRL allergy, although the rate of nonsymptomatic NRL sensitization was considerably higher [26]. In all these patients, clinical symptoms to fruits preceded the history of NRL allergy. The fruits most commonly associated with NRL allergy were banana, peach, and melon. Moreover, all patients who reported problems with foods such as banana, avocado, chestnut, or tomato, were sensitized to NRL.

Additionally, two of 29 patients allergic to fruits or vegetables, who live in an area without birch trees, were clinically allergic to NRL [27]. As expected, patients with allergy to plant-derived food and associated pollinosis showed a high frequency of IgE reactivity to profilins. Taking into consideration that one of the NRL allergens is a profilin, this fact may explain the finding of positive serum IgE determinations to NRL and birch pollen in patients allergic to plant-derived foods, owing to the presence of cross-reactive epitopes [27]. In a recent study, twice as many positive PPTs to foods were found in patients with pollinosis, whether or not they were allergic to NRL, as there were in patients allergic to NRL but not to pollens [28•]. NRL allergy was associated with avocado or banana hypersensitivity, whereas pollinosis was associated with allergy to apple, peach, or celery. These results suggest that concomitant allergy to pollen is an important factor in the determination of which plant-derived foods sensitize latex-allergic patients [28•].

**Table 2. Rate of food hypersensitivity among latex-allergic patients**

| Reference                   | Country | Latex-allergic patients, <i>n</i> | Food sensitization/allergy (diagnostic criteria), % |
|-----------------------------|---------|-----------------------------------|-----------------------------------------------------|
| Blanco <i>et al.</i> [17]   | Spain   | 25                                | 52 (history+PPT)                                    |
|                             | Spain   | 80                                | 45 (history+PPT)                                    |
| Makinen-Kiljunen [18]       | Finland | 31                                | 52 (history)<br>35 (PPT)                            |
| Lavaud <i>et al.</i> [19]   | France  | 17                                | 58 (history+SPT)                                    |
| Delbourg <i>et al.</i> [20] | France  | 16                                | 50 (history)<br>36 (SPT)                            |
| Beezhold <i>et al.</i> [21] | Canada  | 47                                | 36 (history+SPT)<br>70 (SPT)                        |
| Brehler <i>et al.</i> [22]  | Germany | 136                               | 43 (history)<br>69 (IgE)                            |
| Kim and Hussain [23]        | USA     | 137                               | 14 (history+IgE)<br>21 (history)                    |

IgE—specific food IgE determination; PPT—prick by prick test; SPT—skin prick test.

### Identification of the allergens responsible for the latex–fruit cross-reactivity

Cross-reactivity among NRL and various fruits has been fully demonstrated by RAST inhibition, and several common antigens have been identified by immunoblot inhibition experiments. A 30 kDa antigen common to NRL, avocado, and banana has been shown by immunoblotting techniques [19]. In addition, two major banana allergens at 33 and 37 kDa have been identified, and they cross-react with NRL [20].

Although cross-reactivity of NRL allergens with foods has been the objective of investigations for several years, some of the cross-reacting allergens implicated in the latex–fruit syndrome were only recently isolated and well characterized [29••]. Table 1 summarizes some of the cross-reactions of NRL allergens. Cross-reactivity among NRL, tomato, and potato has been ascribed to a 46-kDa NRL allergen, Hev b 7, sharing epitopes with a homologous protein (patatin) identified in potato [21]. However, Hev b 7, patatins, and their homologues appear not to contribute to cross-reactivity in the latex–fruit syndrome [30]. It seems that Hev b 7 is an important allergen for adult patients with NRL allergy, but elucidation of the clinical importance of the cross-reactivity with patatin requires further studies [31]. Another NRL allergen, Hev b 5, shows high homology to an acidic kiwi protein, but no relevant cross-reactivity between these two proteins has been demonstrated [32,33]. Moreover, sera from patients with NRL allergy recognize six epitopes in Hev b 5, but database analysis could not identify similar sequences in kiwi or other plant food proteins [34].

NRL profilin, Hev b 8, is a potential cross-reactive allergen among NRL, plant foods, and pollens, but it is a minor NRL allergen with uncertain clinical relevance [35]. In fact, patients with allergy to plant-derived food and associated pollinosis, frequently sensitized to Bet v 2, show positive

specific IgE to NRL owing to cross-reactive epitopes with NRL profilin, usually with no clinical consequences [27]. Banana profilin has been cloned and expressed, and cross-reactivity to NRL profilin has been demonstrated [36]. We also know that Hev b 9 is a 51-kDa enolase and minor NRL allergen, which cross-react with enolases from certain molds, but not with foods [37]. In the same way, NRL superoxide dismutase, Hev b 10, is a potential cross-reactive—but again, minor—NRL allergen [38].

Class I chitinases from chestnut and avocado have been purified, and a pool of sera from four patients with latex–fruit allergy recognizes these two proteins [39]. These class I chitinases include an N-terminal hevein-like domain in their sequence, which could explain the latex–fruit cross-reactivity. The avocado class I chitinase has been cloned and expressed, and the cross-reactivity with hevein has been demonstrated [40,41]. Furthermore, purified class I chitinases from chestnut and avocado elicited positive skin prick tests (SPTs) in more than 50% of a group of 18 patients allergic to NRL and fruits [42•]. By contrast, SPT with class II chitinases from both foods, which lack the hevein-like domain, showed negative results. Moreover, two major banana allergens have been characterized, and identified also as class I chitinases [43•]. The allergenicity of these banana allergens has been shown in more than 50% of a group of patients with latex–banana allergy [43•], and cross-reactivity with hevein has also been demonstrated [44].

In another study, reactive proteins of 30 to 45 kDa (putative class I chitinases) were recognized by both specific polyclonal antibodies to chitinases and sera from patients with latex–fruit allergy in chestnut, cherimoya, passion fruit, kiwi, papaya, mango, tomato, and flour wheat extracts [45]. Class I chitinase from avocado and an NRL extract strongly inhibited IgE binding by these components when tested in immunoblot inhibition assays. These protein

**Table 3. Food hypersensitivities associated with latex-allergy**

| Group | Definition                                                                      | Foods                                                                                                                                            |
|-------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| I     | Frequent and significant associations                                           | Banana, avocado, kiwi, chestnut                                                                                                                  |
| II    | Other significant associations, but only described in certain studies           | Potato, tomato, shellfish                                                                                                                        |
| III   | Common associations, but number of cases not enough to reach significant levels | Papaya, pineapple, passion fruit, mango, fig, nuts (almond, hazelnut), stone fruits (peach, cherry, apricot), melon, apple                       |
| IV    | Less common associations (continuously growing list)                            | Guava, fish, carrot, pear, strawberry, peanut, pepper, grape, coconut, oregano, sage, dill, condurango bark, milk, spinach, beet, loquat, lychee |

Foods have been grouped in four categories, according to the related definition.

bands were not recognized by a pool of sera from patients allergic to NRL but not to fruits [45]. It is interesting that class I chitinases are inactivated by heating, which could explain why plant foods containing these putative allergens that are consumed after cooking are not associated with the syndrome; but class I chitinase expression is clearly induced by ethylene treatment [46•]. Because ethylene oxide is frequently used to treat plant foods, it could be in part responsible for the growing prevalence of latex–fruit allergy, by inducing chitinase expression.

Cloning and expression of the chestnut class I chitinase has demonstrated that the hevein-like domain includes the main IgE-binding epitopes, although RAST/CAP inhibition assays suggest that relevant epitopes are also harbored in the catalytic domain [47]. Recently, a class I chitinase from NRL, Hev b 11, has been characterized, adding new perspectives to the study of latex–fruit cross-reactions [48]. The question is whether class I chitinases cross-react with hevein, Hev b 11, or both of them. Curiously, a 45-kDa putative chitinase with an N-terminal hevein-like domain, cross-reacting with NRL hevein, has been identified as a potential aeroallergen in *Ficus benjamina* [49]. We have previously mentioned that LTPs have been identified as major allergens in *Prunoideae* fruits [9]. The finding that some latex–fruit allergic patients show *Prunoideae* fruit sensitivity, together with the recent identification of a potentially allergenic LTP from NRL (D.H. Beezhold, personal communication), Hev b 12, suggest that other NRL allergens different from Hev b 6 could be implicated in latex–fruit cross-reactions.

Joint consideration of the data discussed above indicates that class I chitinases may be the panallergens responsible for the latex–fruit cross-reactivity, although other allergens may be involved [42].

## Diagnosis and Practical Management of the Latex–Fruit Syndrome

Clinical assessment of latex–fruit allergy is a difficult task. It requires a detailed history, skin tests, laboratory evaluation, and sometimes food oral challenges [50••]. Although oral challenge tests remain the only way to definitely diag-

nose food allergy, in daily practice and to avoid potentially severe reactions, patients are usually diagnosed on the basis of the clinical history complemented with tests for specific IgE. However, no studies on food oral challenges in latex–fruit allergic patients have been published. Therefore, the estimated diagnostic efficacy of the tests currently used is only tentative, until such studies are available.

In our experience, PPT with the fresh fruits most commonly implicated in the latex–fruit syndrome shows an 80% concordance with the initial clinical diagnose. PPT constitutes an easy, cheap, and reproducible way to confirm the clinical suspicion of a fruit allergy. Considering the fruits separately, the diagnostic efficiency is lower for the PPT with papaya and kiwi (approximately 60%, mainly due to some false-positive results) than for banana, avocado, and chestnut, for which efficiency is approximately 90% [17]. However, commercial extracts for SPTs with the fruits implicated in the syndrome generally show a rather variable diagnostic sensitivity, which can be lower than 40% for some of them, probably owing to liability of cross-reacting allergens. Therefore, diagnostic efficiency should be tested before using them in daily practice. In agreement with our results, other authors have also found a more than 80% concordance between banana PPTs and the clinical diagnosis [20]. Therefore, we suggest using both commercial extracts and PPT with any fruit implicated in a patient's adverse reactions.

In our series of latex–food allergic patients, the diagnostic sensitivity for fruit-specific IgE was 37%, as determined by the ImmunoCAP method (Pharmacia Diagnostics, Sweden), in relation to the clinical history and PPT. It better identified avocado-specific IgE (approximately 80%) than the IgE for the rest of the fruits considered (banana 50%, chestnut 25%, kiwi 20%). In our group of patients, diagnostic specificity for fruit-specific IgE determination was approximately 80% [17]. Other authors have found a sensitivity of 32% for fruit-specific IgE, with a higher sensitivity for avocado (67%) than for the rest of foods [22]. Fifty percent of patients report severe reactions. Diagnostic specificity for fruit-specific IgE determinations was generally better than sensitivity, varying from 55% to 87% depending on the food considered [22].

Summarizing our experience, the diagnosis of the food hypersensitivities associated with NRL allergy should be based on the clinical history, complemented with skin tests that should include PPT with fresh foods [17]. As stated previously, SPT with commercial food extracts shows a very variable diagnostic efficacy, whereas food-specific IgE offers very poor predictive values, at least with respect to the fruits more commonly involved in the syndrome [17,22]. Furthermore, performing batteries of skin tests or specific IgE determinations for screening multiple food allergies in latex-allergic patients with no food allergy history is not recommended, because it is likely to result in confusion.

Every patient who is allergic to NRL, or to one of the foods commonly involved in the syndrome, must be asked about possible adverse reactions to the other foods implicated in the syndrome. In these patients, skin tests (including PPT) should be performed with banana, avocado, chestnut, and kiwi, as well as with all the other foods involved in the patient's adverse reactions. In the case of severe anaphylaxis, a positive skin test is enough for diagnosis. If the adverse food reaction is mild, or if several foods are implicated in a single reaction, careful oral challenge tests should be considered.

Foods involved in the latex-fruit syndrome, but not in adverse reactions for a given patient, should be avoided provided that they elicit a positive skin test and that they are not regularly consumed. Foods tolerated and regularly consumed should not be avoided, even if the skin test is positive, although these patients should be advised of the potential risks. Foods showing negative PPT should not be avoided, and when in doubt, an oral challenge test should be performed. Although management of the fruit hypersensitivity associated to NRL allergy is based solely on exclusion diets, the question remains whether specific NRL immunotherapy—currently under clinical trials—could overcome not only NRL allergy but also associated food hypersensitivity.

## Conclusions

The latex-fruit syndrome is an example of aeroallergen-food cross-reactivity with a clear clinical relevance. It should be kept in mind by all clinicians in order to prevent anaphylactic reactions to foods or NRL. Recent data suggest that class I chitinases, with an N-terminal hevein-like domain, are panallergens responsible for this syndrome, although other allergens could be involved. Future investigations should be focused on the improvement of diagnostic tests and therapeutic approaches for the latex-fruit syndrome. In this context, recombinant panallergens might be useful both for diagnosis and for specific immunotherapy.

## Acknowledgment

The author would like to acknowledge the essential contribution of Drs. G. Salcedo, R. Sánchez-Monge, and A. Díaz-Perales for their work on plant class I chitinases as panallergens, as well as the invaluable collaboration of all the personnel from the Allergy Section of Hospital Dr. Negrín. This work was supported by Fondo de Investigaciones Sanitarias (FIS, grant 00/1019) and by Fundación de la Sociedad Española de Alergología e Inmunología Clínica.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Poley GE, Slater JE: **Latex allergy**. *J Allergy Clin Immunol* 2000, 105:1054–1062.
- A recent review on latex allergy, dealing with several aspects that cover from definition to treatment.
2. Charous BL, Blanco C, Tarlo S, et al.: **Natural rubber latex allergy after 12 years: recommendations and perspectives**. *J Allergy Clin Immunol* 2002, 109:31–34.
- A brief update on the current status of latex allergy and its future perspectives. Some practical recommendations are made.
3. Kurup VP, Fink JN: **The spectrum of immunologic sensitization in latex allergy**. *Allergy* 2001, 56:2–12.
4. Alenius H, Kalkkinen N, Reunala T, et al.: **The main IgE-binding epitope of a major latex allergen, prohevein, is present in its N-terminal 43-amino acid fragment, hevein**. *J Immunol* 1996, 156:618–625.
5. Fritsch R, Ebner C, Kraft D: **Allergenic crossreactivities pollen and vegetable foods**. *Clin Rev Allergy Immunol* 1997, 15:397–404.
6. Vieths S, Scheurer S, Ballmer-Weber B: **Current understanding of cross-reactivity of food allergens and pollen**. *Ann N Y Acad Sci* 2002, 964:47–68.
7. •• Breiteneder H, Ebner C: **Molecular and biochemical classification of plant-derived food allergens**. *J Allergy Clin Immunol* 2000, 106:27–36.
- Modern classification of plant-derived food allergens, including families of pathogenesis related proteins, profilins, enzymes and storage proteins. Specific comments on PR-3 type proteins or basic chitinases are included.
8. Hanninen AR, Mikkola JH, Kalkkinen N, et al.: **Increased allergen production in turnip (Brassica rapa) by treatments activating defense mechanisms**. *J Allergy Clin Immunol* 1999, 104:194–201.
- Using a plant model, an increase in prohevein-like allergen content after treatments activating plant defense mechanisms is demonstrated. This could explain, at least in part, the increase in prevalence of latex-fruit allergy.
9. Sanchez-Monge R, Lombardero M, Garcia-Selles FJ, et al.: **Lipid-transfer proteins are relevant allergens in fruit allergy**. *J Allergy Clin Immunol* 1999, 103:514–519.
10. Valenta R, Duchene M, Ebner C, et al.: **Profilins constitute a novel family of functional plant panallergens**. *J Exp Med* 1992, 175:377–385.
11. M'Raihi L, Charpin D, Pons A, et al.: **Cross-reactivity between latex and banana**. *J Allergy Clin Immunol* 1991, 87:129–130.
12. Lavaud F, Cossart C, Reiter V, et al.: **Latex allergy in patient with allergy to fruit (letter)**. *Lancet* 1992, 339:492–493.
13. Ceuppens JL, Van Durme P, Dooms-Goossens A: **Latex allergy in patient with allergy to fruit (letter)**. *Lancet* 1992, 339:493.
14. de Corres LF, Moneo I, Muñoz D, et al.: **Sensitization from chestnuts and bananas in patients with urticaria and anaphylaxis from contact with latex**. *Ann Allergy* 1993, 70:35–39.
15. Rodríguez M, Vega F, García MT, et al.: **Hypersensitivity to latex, chestnut, and banana**. *Ann Allergy* 1993, 70:31–34.

16. Añibarro B, García-Ara MC, Pascual C: Associated sensitization to latex and chestnut. *Allergy* 1993, 70:130–131.
  17. Blanco C, Carrillo T, Castillo R, et al.: Latex allergy: clinical features and cross-reactivity with fruits. *Ann Allergy* 1994, 73:309–314.
  18. Mäkinen-Kiljunen S: Banana allergy in patients with immediate-type hypersensitivity to natural rubber latex: characterization of cross-reacting antibodies and allergens. *J Allergy Clin Immunol* 1994, 93:990–996.
  19. Lavaud F, Prevost A, Cossart C, et al.: Allergy to latex, avocado pear, and banana: evidence for a 30 kD antigen in immunoblotting. *J Allergy Clin Immunol* 1995, 95:557–564.
  20. Delbourg MF, Guilloux L, Moneret-Vautrin DA, Ville G: Hypersensitivity to banana in latex-allergic patients: identification of two major banana allergens of 33 and 37 kD. *Ann Allergy Asthma Immunol* 1996, 76:321–326.
  21. Beezhold DH, Sussman GL, Liss GM, Chang NS: Latex allergy can induce clinical reactions to specific foods. *Clin Exp Allergy* 1996, 26:416–422.
  22. Brehler R, Theissen U, Mohr C, Luger T: "Latex-fruit syndrome": frequency of cross-reacting IgE antibodies. *Allergy* 1997, 52:404–410.
  23. Kim KT, Hussain H: Prevalence of food allergy in 137 patients. *Allergy Asthma Proc* 1999, 20:95–97.
  24. Blanco C, Carrillo T, Castillo R, et al.: Avocado hypersensitivity. *Allergy* 1994, 49:454–459.
  25. Carrillo T, Blanco C, Quirarte J, et al.: Prevalence of latex allergy among greenhouse workers. *J Allergy Clin Immunol* 1995, 96:699–701.
  26. García JC, Moyano JC, Alvarez M, Bellido J: Latex allergy in fruit-allergic patients. *Allergy* 1998, 53:532–536.
  27. Díez-Gómez ML, Quirce S, Cuevas M, et al.: Fruit-pollen-latex cross-reactivity: implication of profilin (Bet v 2). *Allergy* 1999, 54:951–961.
  - 28.● Levy DA, Mounedji N, Noirot C, Leynadier F: Allergic sensitization and clinical reactions to latex, food and pollen in adult patients. *Clin Exp Allergy* 2000, 30:270–275.
- A very interesting clinical study that tries to discern the relationship among latex, pollen, and food allergies in adult patients.
- 29.● Salcedo G, Diaz-Perales A, Sánchez-Monge R: The role of plant panallergens in sensitization to natural rubber latex. *Curr Opin Allergy Clin Immunol* 2001, 1:177–183.
- An excellent review article on the plant panallergens implicated in latex-fruit cross-reactivity.
30. Sowka S, Hafner C, Radauer C, et al.: Molecular and immunologic characterization of new isoforms of the hevea brasiliensis latex allergen Hev b 7: evidence of no cross-reactivity between Hev b 7 isoforms and potato patatin and proteins from avocado and banana. *J Allergy Clin Immunol* 1999, 104:1302–1310.
  31. Seppala U, Palosuo T, Seppala U, et al.: IgE reactivity to patatin-like latex allergen, Hev b 7, and to patatin of potato tuber, Sol t 1, in adults and children allergic to natural rubber latex. *Allergy* 2000, 55:266–273.
  32. Akasawa A, Hsieh LS, Martin BM, et al.: A novel acidic allergen, Hev b 5, in latex: purification, cloning and characterization. *J Biol Chem* 1996, 271:25389–25393.
  33. Slater JE, Vedvick T, Arthur-Smith A, et al.: Identification, cloning, and sequence of a major latex allergen (Hev b 5) from natural rubber latex (*Hevea brasiliensis*). *J Biol Chem* 1996, 271:25394–25399.
  34. Beezhold DH, Hickey VL, Slater JE, Sussman GL: Human IgE-binding epitopes of the latex allergen Hev b 5. *J Allergy Clin Immunol* 1999, 103:1166–1172.
  35. Ganglberger E, Radauer C, Wagner S, et al.: Hev b 8, the Hevea brasiliensis profilin, is a cross-reactive allergen of latex, plant foods and pollen. *Int Arch Allergy Immunol* 2001, 125:216–227.
  36. Reindl J, Rihs HP, Scheurer S, et al.: IgE reactivity to profilin in pollen-sensitized subjects with adverse reactions to banana and pineapple. *Int Arch Allergy Immunol* 2002, 128:105–114.
  37. Wagner S, Breiteneder H, Simon-Nobbe B, et al.: Hev b 9, an enolase and a new cross-reactive allergen from hevea latex and molds: purification, characterization, cloning and expression. *Eur J Biochem* 2000, 267:7006–7014.
  38. Wagner S, Sowka S, Mayer C, et al.: Identification of a Hevea brasiliensis latex manganese superoxide dismutase (Hev b 10) as a cross-reactive allergen. *Int Arch Allergy Immunol* 2001, 125:120–127.
  39. Diaz-Perales A, Collada C, Blanco C, et al.: Class I chitinases with hevein-like domain, but not class II enzymes, are relevant chestnut and avocado allergens. *J Allergy Clin Immunol* 1998, 102:127–133.
  40. Sowka S, Hsieh LS, Krebitz M, et al.: Identification and cloning of Prs a 1, a 32 kDa endochitinase and major allergen of avocado, and its expression in the yeast *Pichia pastoris*. *J Biol Chem* 1998, 273:28091–28097.
  41. Chen Z, Posch A, Cremer R, et al.: Identification of hevein (Hev b 6.02) in Hevea latex as a major cross-reacting allergen with avocado fruit in patients with latex allergy. *J Allergy Clin Immunol* 1998, 102:476–481.
  - 42.● Blanco C, Diaz-Perales A, Collada C, et al.: Class I chitinases are major panallergens responsible for the latex-fruit syndrome. *J Allergy Clin Immunol* 1999, 103:507–513.
- A study using purified chitinases from chestnut and avocado, demonstrating that they are major allergens implicated in latex-fruit cross-reactivity.
- 43.● Sanchez-Monge R, Blanco C, Díaz-Perales A, et al.: Isolation and characterization of relevant banana allergens: identification as fruit class I chitinases. *Clin Exp Allergy* 1999, 29:673–680.
- Identification of class I chitinases as major banana allergens cross-reacting with latex.
44. Mikkola JH, Alenius H, Kalkkinen N, et al.: Hevein-like protein domains as a possible cause for allergen cross-reactivity between latex and banana. *J Allergy Clin Immunol* 1998, 102:1005–1012.
  45. Diaz-Perales A, Collada C, Blanco C, et al.: Cross-reactions in the latex-fruit syndrome: a relevant role of chitinases but not of complex asparagine-linked glycans. *J Allergy Clin Immunol* 1999, 104:681–687.
  - 46.● Sanchez-Monge R, Blanco C, Díaz-Perales A, et al.: Class I chitinases, the panallergens responsible for the latex-fruit syndrome, are induced by ethylene treatment and inactivated by heating. *J Allergy Clin Immunol* 2000, 106:190–195.
- An experimental model to demonstrate different expression of chitinases depending on plant growing — or food processing — conditions. Its clinical implications should be carefully considered.
47. Diaz-Perales A, Sánchez-Monge R, Blanco C, et al.: What is the role of the hevein-like domain of fruit class I chitinases in their allergenic capacity?. *Clin Exp Allergy* 2002, 32:448–454.
  48. O'Riordain G, Radauer C, Hoffman-Sommergruber K, et al.: Molecular characterisation and cloning of the Hevea brasiliensis allergen Hev b 11, a class I chitinase. *Clin Exp Allergy* 2002, 32:455–462.
  49. Chen Z, Duser M, Flagge A, et al.: Identification and characterization of cross-reactive natural rubber latex and *Ficus benjamina* allergens. *Int Arch Allergy Immunol* 2000, 123:291–298.
  - 50.● Sicherer SH: Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol* 2001, 108:881–890.
- A comprehensive review focused on clinical aspects of cross-reacting food allergens, with special mention of the latex-food allergy.