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Repeated anaphylactic episodes to orange and apple

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SUMMARY

This study reports an unusual case of repeated anaphylactic episodes to orange and apple without clinical evidence of primary sensitization to peach LTP. In vitro and in vivo tests revealed heat stability of the implicated allergens and also provided new evidence of differences in allergenicity among apple varieties and strong cross reactivity of citrus fruits. "Prick-to-prick" method with fresh fruits proved to be a quick and advantageous tool in investigating allergy to fresh fruits.

Introduction

Allergy to apple, a fruit of the *Rosaceae* botanical family, is usually demonstrated with mild oropharyngeal symptoms. Systemic manifestations mainly occur in the Mediterranean area and are thought to be based on cross-reactivity between apple lipid transfer protein (LTP) Mal d 3 and peach LTP Pru p 3, with the latter considered as the primary sensitizer (1). Anaphylaxis to orange, a *Rutaceae* fruit, is very rare and has been assumed to depend mainly on sensitization to another LTP, Cit s 3 (2, 3). No clinical association between these two disparate botanical families has been reported.

Case Report

A 38-year-old man who suffered from 5 repeated anaphylactic episodes, 3 to orange and 2 to apple, was referred to

our department for allergological assessment. He reported to have developed palms and face itching, flushing, facial angioedema, hoarseness, dyspnoea and dizziness within 20 to 60 minutes after the ingestion of a raw orange a year before. Emergency therapy and short hospitalization were required. Subsequently, in an attempt to confirm himself anaphylaxis to orange, he consumed separately a small amount of a fresh orange and fresh orange juice. A clinical reaction similar to the initial one was induced in both occasions. Six months after his first anaphylactic episode to orange, he experienced the same consecutive symptoms, but more intense, after having eaten a raw Granny Smith apple. Interestingly, apple had been well tolerated priorly and after anaphylaxis to orange. A month later, in a way of self-food-challenge again, intake of a small amount of apple was followed by an immediate systemic reaction of the same clinical severity. His history, apart from seasonal allergic rhinitis, revealed oral allergy syndrome to peach, grapes, wine and bell pepper.

Prick-to-prick tests (4) with fresh, raw and boiled (isolated entire fruit at 100°C for 30 minutes) 4 apple cultivars were positive for raw and boiled Granny Smith and Starking Delicious, raw Jonagold and Royal Gala but negative for boiled Jonagold and Royal Gala. Prick to prick tests with fresh, raw and boiled, orange and 3 other citrus fruits (lemon, mandarin, grape fruit), all induced strong skin reactivity. Commercial orange juice elicited a positive response too. Skin prick tests (SPTs) with commercial extracts provided positive results for orange, peach, apricot, marginally positive for apple and negative for grapes. SPTs with common aeroallergens were positive for cypress, mugwort and negative for birch. Histamine at 10 mg/mL and normal saline 0,9% were used as a positive and negative control, respectively. Skin reactions were measured at 15-20 minutes and considered positive if the diameter of the wheal was > 3 mm compared to the negative control and accompanied by erythema (table 1). Total immunoglobulin E (IgE) was 34,70 IU/mL and

serum tryptase was 1µg/L. Specific IgE (CAP System, Phadia) was moderately positive for orange (0,84, class II) and peach (0,74, class II) and negative for apple as well as pear, grapes and latex.

For ethical reasons, after considering a convincing history of recent severe anaphylaxis, our patient did not undergo oral provocations tests with apple and orange.

Discussion

Positive prick-to-prick tests with both raw and boiled orange and 2 apple varieties suggest heat-stability of the allergens involved. Two classes of plant allergens possess such stability, LTPs and thaumatin-like proteins (TLPs). Mal d 3 has been commonly reported as the responsible agent for apple anaphylaxis (1, 5). The clinical relevance of TLPs has not yet been established. Even though the culprit allergen has not been confirmed and the implica-

Table 1 - Skin tests with commercial extracts, raw and boiled fresh fruits

Fruits	SPTs	Prick to prick with raw fruits	Prick to prick with boiled fruits
A P P L E	Granny smith Starkin delicious Royal gala Jonagold	5/25 7/30 5/32 6/20	5/20 4/10 2,5/(-) 2,5/(-)
Orange	8/30	9/26	7/29
Mandarin	Not done	5/9	4/8
Lemon	Not done	10/35	7/32
Grapefruit	Not done	5/11	4/10
Commercial orange juice			4/11
Peach	7/35	Out of season / not done	Out of season / not done
Apricot	4/15	Out of season / not done	Out of season / not done
Grapes	-/-	Out of season / not done	Out of season / not done
<i>Aeroallergens</i>			
Cypress	6/12		
Mugwort	5/11		
Birch, olea, parietaria, grasses, acer, poplar, platanus, willow, ambrosia, chenopodioum, plantain, dandelion, alternaria, mites, cat, dog, latex	-/-		
Histamine	6/23		
N/S 0,9%	-/-		

*Mean wheal diameter / erythema diameter in mm

tion of Mal d 3 can only be hypothesized by the available clinical and *in vivo* data, it is of critical significance to notice that orange, not peach, was the first triggering food in our case. In fact, in a series of studies on *Rosaceae* fruit allergy in the Mediterranean area, peach has been shown as the first triggering food to subsequently associate other *Rosaceae* fruits, such as apple, due to cross-reactivity of their LTPs (1, 6). Our patient suffered repeated anaphylactic episodes to apple but only OAS to peach ingestion. Although sensitization to peach LTP is not obligingly synonymous to severe symptoms, manifestation of anaphylaxis to apple intake renders this potential sensitization unlikely as the primary one. Whether severe clinical symptoms are going to be induced by peach in the future remains to be revealed. Differences in the route of sensitization might be related to genetic factors (not known so far) or dietary habits. Our patient mentioned to have usually consumed orange juice and apples but not peach. A study concerning the prevalence and the development as well as the sensitization patterns of food allergy to *Rosaceae* in Greek population is still lacking. LTP sensitive patients with *Rosaceae* allergy may manifest adverse reactions after the ingestion of a large spectrum of non-*Rosaceae* plant-derived foods including hazelnut, walnut, and peanut (7). Cross-reactivity between Cit s 3 and Pru p 3, relating two distant botanical families, has been shown (8), but its clinical relevance remains obscure.

Differences in prick-to-prick results among apple varieties are indicative of differences in their antigenic and allergenic profiles. Starking Delicious and Royal Gala varieties induced the strongest and the weakest skin reactivity respectively in consistency with a study on apple allergenicity in which the Starking variety provided the largest wheals and Royal Gala provided the lowest specific IgE titers (9). Positivity extended to all citrus members tested, raw and boiled, implies strong cross-reactivity and heat stability of the implicated allergens as also pointed elsewhere (3, 8).

In this patient, allergic to heat-stable allergens, prick-to-prick tests with fresh and boiled fruits were more efficacious than SPT with the commercial extract in detecting IgE sensitization to apple. CAP System seemed not to be reliable on confirming clinical sensitization to apple and orange as the patient is Bet v 1 negative, so the low specific IgE levels to these fruits are suggestive of a heat-stable allergen sensitization generally present in a lower con-

centration in CAP extract. Our results emphasize the importance of "prick-to-prick" method in investigating fruit allergy (10).

In summary, we present an exceptional case of anaphylaxis to two botanically distant fruits, apple and orange, without clinical evidence of primary sensitization to peach LTP. We provided new evidence of differences in allergenicity among apple varieties not depending on Bet v 1 homologous and strong cross-reactivity of citrus fruits. "Prick-to-prick" method with fresh and cooked fruits proved to be in some cases a quick and advantageous tool in investigating allergy to fresh fruits.

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