

Oral Allergy Syndrome to Fig

A. Antico^a G. Zoccatelli^b C. Marcotulli^a A. Curioni^c

^aAzienda Istituti Ospedalieri 'C. Poma' – Mantova, Servizio Autonomo di Allergologia, Ospedale di Asola, Mantova,

^bDipartimento Scientifico e Tecnologico, Università di Verona, Verona, and ^cDipartimento di Biotecnologie Agrarie, Università di Padova, Legnaro, Italia

Key Words

Ficus carica · Fig allergy · Fig allergens · Oral allergy syndrome

Abstract

Background: The few cases of food allergy to fig reported to date, whose main manifestations were anaphylactic reactions, have been related to a cross-sensitisation to weeping fig (*Ficus benjamina*) or to the 'latex-fruit syndrome'. Here we report on two cases of the oral allergy syndrome (OAS) to fig in patients whose main allergic manifestations were related to sensitisation to grass and birch pollens. **Methods:** The patients were characterised by clinical history, skin prick tests (SPT) with commercial and in-house extracts, prick-by-prick test, specific IgE measurements and challenge tests. PBS-soluble and insoluble extracts of both fig skin and pulp were examined for the presence of potential allergens by IgE immunoblotting. **Results:** Both patients showed OAS followed by respiratory symptoms when challenged with fig. They were negative in both specific IgE detection and SPT with commercial extracts of fig and many other plant materials, including *F. benjamina* and *Hevea brasiliensis*, while grass and birch pollens gave positive results. Prick-by-prick tests and SPT with in-house extracts indicated that the fig skin had a much higher allergenicity than the pulp. Despite negative IgE

detection by the CAP assay, immunoblotting experiments showed that potential fig allergens were PBS-soluble and present only in the skin of the fruit. **Conclusions:** OAS to fig followed by respiratory symptoms can be present in patients not sensitised to weeping fig or having the latex-fruit syndrome. Different parts of the fig can have different allergenicities, the most important allergens being proteins related to the skin of the fruit. Improved commercial fig extracts to be used for the diagnosis of this type of allergy have to be developed.

Copyright © 2003 S. Karger AG, Basel

Introduction

The fig, the (false) fruit of *Ficus carica*, has rarely been reported to be the cause of food allergy. Only recently, a few scientific reports have indicated the fig as a plant food causing allergic manifestations, most of them being related to cross-sensitisation to the weeping fig (*Ficus benjamina*), an ornamental plant belonging to the same *Moraceae* family [1–4]. The fig has also been included among those plant foods responsible for the 'latex-fruit syndrome', an allergic disease resulting from cross-sensitisation to *Hevea brasiliensis* latex and several types of fruits [5, 6].

In the present study we report two cases of food allergy to fig with distinctive features compared to the ones previously described.

KARGER

Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2003 S. Karger AG, Basel
1018–2438/03/1312–0138\$19.50/0

Accessible online at:
www.karger.com/iaa

Correspondence to: Prof. Andrea Curioni
Dipartimento di Biotecnologie Agrarie
Università di Padova, Strada Romea 16
I–35020 Legnaro (PD) (Italy)
Tel./Fax +39 049 82729219, E-Mail andrea.curioni@unipd.it

Materials and Methods

Patients

Case 1. Patient 1 was a 27-year-old white woman with a personal history of atopy. For 3 years she had suffered from seasonal allergic rhinitis with secondary symptoms of asthma resulting from allergic sensitisation to grass and birch pollens. Moreover, the patient complained of light local symptoms of the oral allergy syndrome (OAS) [7] after eating apple, peach and kiwi fruits. Recently, the patient reported the onset of oral symptoms after the ingestion of a fig, which was previously tolerated. Further exposure to this fruit resulted in a gradual exacerbation of the oral symptoms. The last time the patient ate a fig, the oral symptoms were followed by rhinoconjunctivitis, mild oedema of the eyelids and lips, and burning of the throat. She took one antihistamine pill and recovered in a short time.

Case 2. Patient 2 was a white 34 year-old woman with a history of seasonal rhinitis with secondary symptoms of asthma resulting from allergic sensitisation to grass and birch pollens. The patient suffered from OAS after eating apple, pear, peach and hazelnut. Recently she had allergic symptoms after eating a fig, which was previously tolerated. While chewing the fig, the patient felt strong itching of the mouth, followed by severe conjunctivitis and rhinitis, sore throat and then wheezing, dyspnoea and oedema of lips and face.

She was treated with corticosteroids and antihistamines and salbutamol MDI in the emergency ward. The symptoms gradually improved and disappeared completely after a few hours.

Sample Preparation

A fig was peeled with a knife, as is normally done before eating this fruit. In this way, the 'skin' fraction comprised both the green external layer of pigmented cells and a part of the whitish underlying tissue. A sample of the pulp (the red internal part of the fig) was also separated.

The skin and the pulp were extracted with PBS (1:4 w:v) for 15 min at 4°C. After centrifugation (12,000 g for 15 min at 4°C), the clear supernatants (containing 3 and 1 mg of protein/ml for the skin and the pulp, respectively) were collected and stored at -20°C. These extracts were also used in skin prick tests (SPT; see below). The residues of the PBS extraction were treated 1:4 (w:v) with a 0.1 M Tris-HCl buffer, pH 7.6, containing 2% (w:v) sodium dodecyl sulphate (SDS) and 2% (v:v) 2-mercaptoethanol in a boiling water bath for 10 min. After centrifugation, the supernatants made up the 'PBS-insoluble fraction' that was stored at -20°C.

Sodium Dodecyl Sulphate-Polyacrylamide Gel Electrophoresis and Immunoblotting

SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting were performed as previously described [8].

Briefly, after SDS-PAGE separation in a 14% total polyacrylamide gel, fig proteins were electroblotted onto a polyvinylidene difluoride membrane. Membranes were then incubated overnight with patient sera diluted 1:3 with PBS. After washing, the membranes were treated with an anti-human IgE peroxidase-conjugated antibody (Sigma, Milan, Italy). After further washing peroxidase activity was revealed by chemiluminescence using the SuperSignal detection kit (Pierce, Rockford, Ill. USA).

Skin Tests and Specific IgE Measurements

SPT were performed with a complete set of commercially available allergens (Lofarma, Milan, Italy). Besides the common respira-

tory and food allergens, commercial extracts of peach, apple, kiwi, banana, chestnut, latex and weeping fig were also tested. Skin tests for the plant foods the patients reported to be responsible for the allergic manifestations were repeated with the prick-by-prick technique. The fig test was performed with both the skin and the pulp of a green fig and also by using the PBS extracts prepared as described above.

Specific IgE were measured with the CAP-FEIA system (Pharmacia, Uppsala, Sweden) according to the manufacturer's instructions.

Challenge Tests

Challenge tests were performed with a green fig, after the patients' informed consent. Considering the difficulties in masking this food, the tests were carried out in an open way according to the guidelines of the Italian Society of allergy and Clinical Immunology [9].

About 20 g of a normally knife-peeled green fig were chewed for 1 min and spat out in order to avoid ingestion. Respiratory functionality was measured before challenge and at 15-min intervals after the onset of the allergic symptoms.

The challenge test was performed when FEV₁ values were not inferior to 10% of the theoretical reference value and average nasal resistance not superior to 30 Pa. The test was regarded as positive if there was a drop in the FEV₁ equal or superior to 15% and an increase in the average nasal resistance values (R_m) by at least twice as much as the basal ones and a decrease in the average nasal flux (F_m) by at least 50% [9].

Results

The main laboratory data and prick test results for the two cases examined in this study are summarised in table 1. Both patients showed positivity in skin tests with grass and birch pollens, while SPTs with commercial extracts of all the other allergenic plant materials tested, including peach, apple, banana, kiwi, latex and weeping fig, were negative. Instead, prick-by-prick tests with peach and apple were positive. Patient 1, but not patient 2, was also positive to prick-by-prick test with a kiwi fruit. Prick-by-prick tests carried out with the skin fraction of a green fig gave a strong positivity in both patients, with a cutaneous reaction higher than that induced by the positive histamine control, while only a minimal reaction (slightly higher than that of the negative PBS control) was noticed when the fig pulp was pricked in the same way. These results were confirmed by pricking the fresh PBS extracts (at 1 mg/ml of protein) of both fig skin and pulp. Also in this case the skin extract provoked a strong reaction, whereas the pulp induced a weak cutaneous response, only slightly higher than that of PBs. SPTs with the same PBS extracts in 5 control patients sensitised to grass and/or birch pollens were negative.

Specific IgE measurements confirmed the presence of high IgE levels to grass and birch pollens, and peach, while

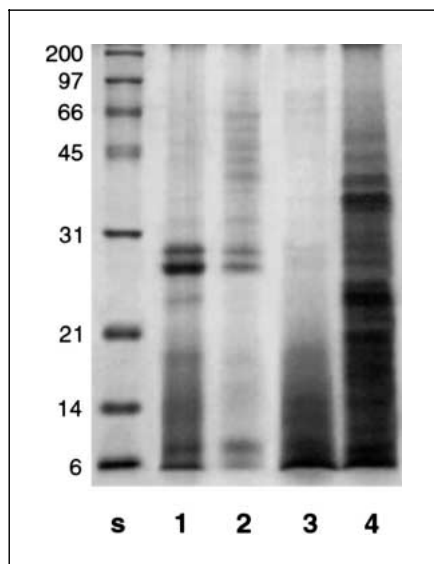


Fig. 1. SDS-PAGE analysis of fig proteins. Lanes 1 and 2 show PBS-soluble proteins from fig skin and pulp, respectively. Lanes 3 and 4 show PBS-insoluble proteins from fig skin and pulp, respectively. Molecular weight standard proteins are in lane s.

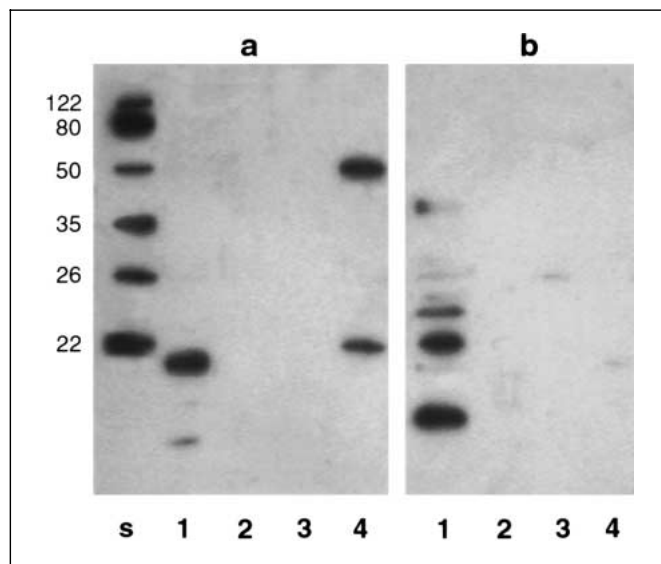


Fig. 2. Binding to fig proteins of IgE antibodies from sera of patient 1 (a) and patient 2 (b). Lanes 1 and 2 show PBS-soluble proteins from fig skin and pulp, respectively. Lanes 3 and 4 show PBS-insoluble proteins from fig skin and pulp, respectively. Molecular weight standard proteins are in lane s.

Table 1. Summary of the main laboratory data and skin test results

	Case 1 ^a			Case 2 ^b		
	specific IgE kU/l	class	SPT	specific IgE kU/l	class	SPT
Grass (mix)			++			+++
<i>Phleum pratense</i>	1.50	2	+	47.84	4	+++
<i>Cynodon dactylon</i>	2.00	2	++	9.97	3	+++
<i>Lolium perenne</i>	1.93	2	++	36.44	4	+++
Birch	21.03	4	++++	8.72	3	+++
Apple	0.10	0	(-)(+)	0.00	0	(-)(+)
Peach	2.60	2	(-)(+)	0.60	1	(-)(+)
Kiwi	0.00	0	(-)(+)	0.00	0	(-)
Banana	0.00	0	(-)	0.00	0	(-)
Chestnut	0.00	0	(-)	0.00	0	(-)
Papain	0.00	0	(-)	0.00	0	(-)
Latex	0.00	0	(-)	0.00	0	(-)
Weeping fig	0.00	0	(-)	0.00	0	(-)
<i>Fig fruit</i>						
IgE assay	0.00	0		0.00	0	
Prick-by-prick, pulp			negative			negative
Prick-by-prick, skin			+++			++++
IgE immunoblot, pulp	negative			negative		
IgE immunoblot, skin	positive (<10, 20 kD)			positive (10, 22, 24 kD)		

IgE assays were done by the CAP-FEIA system. (-) = Negative SPT with commercial extracts; (+) = positive skin test with fresh fruits (prick-by-prick).

^a Total IgE: 156.60 kU/l.

^b Total IgE: 63.70 kU/l.

no IgE to latex, papain, chestnut, banana, kiwi, apple, weeping fig and fig fruit was detected by the CAP-FEIA system. The oral challenge tests with fig were positive in both patients. Symptoms appeared approximately 10 min after challenge. For patient 1, the oral mucosal symptoms were followed by conjunctivitis, eyelid and lip oedema and slight rhinitis with nasal obstruction, which, however, did not reach significant levels ($R_m = +71\%$; pre- and postchallenge, FEV_1 unchanged). For patient 2, the oral symptoms were followed by rhinoconjunctivitis and asthma with significant nasal obstruction and bronchospasm ($R_m = +429\%$, $F_m = -52\%$; $FEV = -21\%$). The symptoms were controlled with salbutamol MDI and antihistamines and steroids.

The PBS-soluble and PBS-insoluble proteins extracted from both the fig skin and pulp were separated by SDS-PAGE (fig. 1) and tested by IgE immunoblotting with the sera of the 2 allergic patients. The results (fig. 2) showed the presence of IgE binding to PBS-soluble protein bands of the fig skin, although the bands bound by the IgE of the two sera were different in both number and, though slightly, electrophoretic mobility. A major band of about 20 kD plus a minor band with a lower molecular weight were recognised in the skin extract by the serum IgE of patient 1 (fig. 2a, lane 1), while three bands (M_r s of about 10, 22 and 24 kD) were detected by using the serum of patient 2 (fig. 2b, lane 1). No IgE-binding bands were found in the PBS-soluble fraction of the fig pulp (fig. 2, lanes 2), confirming the results of the skin tests. However, two bands were recognised by the serum IgE of patient 1 in the PBS-insoluble fraction of the pulp (fig. 2a, lane 4), thus indicating that some potential allergens cannot be extracted from the fig in nondenaturing conditions. On the contrary, no PBS-insoluble IgE-binding bands could be detected in the skin samples (fig. 2, lanes 3). No IgE-binding bands were detectable when the sera of two healthy subjects were used in control experiments (not shown).

Discussion

The OAS is a distinctive type of allergic reaction to foods which results from the direct contact of the allergenic food with the oral mucosa [10, 11]. The cases described here are two classical examples of OAS followed by systemic respiratory symptoms. For both examined patients, challenge tests confirmed that the events eliciting the allergic response occurred in the mouth, because the food was only chewed for some time and then spat out, thus avoiding its ingestion. Therefore, in our patients, the

clinical manifestations of allergy to fig were different from those of other cases reported, in which anaphylactic reactions without OAS were the major allergic symptoms [1–6].

So far food allergy to fig has been mainly interpreted as a result of a cross-reaction in patients sensitised to weeping fig (*F. benjamina*), an ornamental plant taxonomically close to fig (*F. carica*), by the inhalatory route [1–4]. In other cases, the fig has been reported to be one of the plant foods involved in the latex-fruit syndrome [5, 6]. On the other hand, in the cases described in this study, the OAS symptoms appeared to occur in patients whose main allergic manifestations derived from sensitisation to pollens of plants not related to fig, as suggested by clinical histories, SPT and specific IgE detection. Moreover, allergic symptoms to weeping fig or to latex were clinically absent and sensitisation to these plant materials was not found by SPT and/or specific IgE detection. These observations suggest that sensitisation to fig in our patients could have occurred as a primary event, although a cross-reactivity with pollens cannot be completely excluded.

Another interesting aspect, not investigated previously, concerns the much stronger cutaneous reactions resulting from the fig skin compared to those induced by the pulp. In both patients, these different reactions were obtained by both prick-by-prick and SPT tests with PBS extracts of the two parts of the fig fruit. Moreover, immunoblotting experiments confirmed the presence of IgE binding proteins in the PBS-soluble fractions of the skin, whereas the PBS extract of the pulp did not show any potential allergens (fig. 2). The fig fruit is technically a syconium, that is an unusual multiple fruit constituted by a hollow receptacle with hundreds of small fleshy flowers facing each other on the inside. Therefore, in our patients, the allergic symptoms seem to be due to components present in the receptacle (skin), whereas the flowers (the internal red part of the fig) do not appear to be allergenic. Figs are sometimes eaten with the skin. If not, the skin is only partly removed by peeling, and therefore is actually put into the mouth when the (peeled) fig is eaten, thus possibility causing the OAS symptoms. The prevalence of allergenic proteins in the external layers is a common feature of allergenic fruits, as in the case of *Rosaceae*, for example [12]. Several plant allergens correspond to proteins having a defence role in the plant [13]. Since the peel of the fruit is a barrier for the action of predators or parasites present in the external environment, its content in defence proteins should be quantitatively or qualitatively different from that of the internal pulp [12]. According to the results presented here, this view seems to also apply to

the syconium of the fig. This fact should be considered in both the clinical evaluation of the patients and also in the preparation of the extracts to be used for the diagnosis of allergy to fig.

Fig allergens have not been characterised previously. By immunoblotting with sera of allergic patients, we have identified here the apparent molecular weights and solubility properties of potential allergens of the fig fruit. Though the 2 patients examined had similar clinical features, they did not show IgE binding to the same protein bands in immunoblotting, which indicates that OAS symptoms can be induced by different potential allergens present in the PBS-soluble fraction of the fig skin. Moreover, patient 1, but not patient 2, had IgE recognising two protein bands of the pulp that are insoluble in PBS. These latter proteins are, therefore, unlikely to act in the aqueous environment of the mouth, although insoluble food proteins may be involved in allergic responses at the gastrointestinal level, because the digestion process can change their solubility properties [14].

Though showing IgE binding to some fig proteins in immunoblotting, the allergic patients studied were both negative in fig-specific IgE detection by CAP-FEIA. This system therefore, seems to be insensitive in detecting pri-

mary allergy to fig in patients without sensitisation to *F. benjamina* and *H. brasiliensis*. The possibility of negative results in detecting specific IgE involved in food allergies has often been reported [8, 14, 15]. This can be due to loss or modification of specific allergens during the preparation of the foods extracts to be used in the different diagnostic assays, which, for this reason, can have a poor predictive value in confirming or ruling out a food allergy [14–16]. In particular, in the case of the fig, it is possible that the allergens of the skin were not considered in preparing the diagnostic extracts. The results described here also confirm the poor predictive value of the in vitro specific IgE detection for allergy to fig and indicate that the diagnosis of this type of allergy can be made more precisely by using the prick-by-prick technique or preparing simple fresh extracts of the fruit to be used in SPT.

In conclusion, we have reported two cases of OAS from fig, which could be caused by allergens present in the skin. These cases widen the spectrum of the clinical presentation of allergy to fig, as reported in the literature so far. The lack of cross-reactivity with weeping fig, latex and other plant materials involved in the latex-fruit syndrome suggests that different allergens could be responsible for the different clinical manifestations of food allergy to fig.

References

- 1 Dechamp C, Bessot JC, Pauli G, Deviller P: First report of anaphylactic reaction after fig (*Ficus carica*) ingestion. *Allergy* 1995;50:514–516.
- 2 Diez-Gomez ML, Quirce S, Aragonese E, Cuevas M: Asthma caused by *Ficus benjamina* latex: Evidence of cross-reactivity with fig fruit and papain. *Ann Allergy Asthma Immunol* 1998;80:24–30.
- 3 Oei HD, Tjiook SB: A case report of an anaphylactic reaction after fig (*Ficus carica*) ingestion. *Allergy* 1998;53:85.
- 4 Gandolfo M, Baeza M, De Barrio M: Anaphylaxis after eating fig. *Allergy* 2001;56:462–463.
- 5 Blanco C, Carrillo T, Castillo R, Quiralte J, Cuevas M: Latex allergy: Clinical features and cross-reactivity with fruits. *Ann Allergy* 1994;73:309–314.
- 6 Brehler R, Theissen U, Mohr C, Luger T: Latex-fruit syndrome: Frequency of cross-reacting IgE antibodies. *Allergy* 1997;52:404–410.
- 7 Johansson SGO, Hourihane JO, Bousquet J, et al: A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813–824.
- 8 Pasini G, Simonato B, Giannattasio M, Gemignani C, Curioni A: IgE binding to almond proteins in two CAP-FEIA-negative patients with allergic symptoms to almond as compared to three CAP-FEIA-false-positive subjects. *Allergy* 2000;55:955–958.
- 9 Memorandum sulla diagnostica delle allergopatie. SIAIC position statement. *G Ital Allergol Immunol Clin* 1992;2:351–370.
- 10 Amlot PL, Kemeny DM, Zachary C, et al: Oral allergy syndrome (OAS): Symptoms of IgE-mediated hypersensitivity to foods. *Clin Allergy* 1987;17:33–42.
- 11 Ortolani C, Ispano M, Pastorello E, et al: The oral allergy syndrome. *Ann Allergy* 1988;61:47–52.
- 12 Fernandez-Rivas M, Cuevas M: Peels of Rosaceae fruits have a higher allergenicity than pulps. *Clin Exp Allergy* 1999;29:1239–1247.
- 13 Ebner C, Hoffmann-Sommergruber K, Breiteneder H: Plant food allergens homologous to pathogenesis-related proteins. *Allergy* 2001;56(suppl 67):43–44.
- 14 Simonato B, De Lazzari F, Pasini G, Polato F, Giannattasio M, Gemignani C, Peruffo AD, Santucci B, Plebani M, Curioni A: IgE binding to soluble and insoluble wheat flour proteins in atopic and non-atopic patients suffering from gastrointestinal symptoms after wheat ingestion. *Clin Exp Allergy* 2001;31:1771–1778.
- 15 Pastorello E: Oral allergy syndrome: Clinical aspects and pathogenetic mechanisms. *Semin Clin Immunol* 1992;4:35–40.
- 16 Ortolani C, Ispano M, Pastorello EA, Ansaloni R, Magri GC: Comparison of results of skin prick tests (with fresh foods and commercial extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol* 1989;83:683–690.