

Allergy to minor allergens of Brazil nut

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Key words: 2S albumins; Brazil nut; food allergy; seed storage proteins; urticaria.

ALTHOUGH INFREQUENT, allergy to Brazil nut (*Bertholletia excelsa*) has become quite famous as a model of experimental transfer of an allergen into a transgenic crop plant (1).

Recent studies found that sensitization to the major Brazil nut allergen, Ber e 1,

a 9 kDa methionine-rich 2S albumin (2), is correlated with the clinical expression of allergy, whereas patients sensitized to minor allergens do not have allergic symptoms (3).

The findings of our study seem to contradict this statement. A 15-year-old boy with a history of "atopic eczema" in early childhood, and of both birch and grass pollen allergy since the age of 4, experienced two distinct episodes of generalized urticaria about 30 min after ingesting a Brazil nut. He reported a history of typical, slight oral allergy syndrome immediately after eating hazelnut, but tolerated all other fresh fruits and vegetables.

Skin prick tests (SPT) with commercial extracts of main airborne allergens confirmed both birch and grass pollen hypersensitivity, and showed sensitization to pellitory pollen, as well as cat dander. SPT with a large series of commercial vegetable food extracts (Dome-Hollister/Stier 1 : 10 w/v) showed marked skin reactivity to Brazil nut (mean wheal diameter 20 mm), a slight to moderate reactivity to pea, soybean, celery, and almond (2-3 mm), and no reac-

tivity to walnut, tomato, carrot, potato, plum, and bean. SPT with fresh apple were negative, but fresh hazelnut induced a moderate (3 mm) response. Extracts of Brazil nut, birch pollen, hazelnut, peanut, and of a series of foods containing 2S albumin (mustard, poppy seed, sesame seed, sunflower seed) were prepared as previously described (4). The final protein concentrations were: Brazil nut 20.4 mg/ml, birch pollen 660 mg/ml, hazelnut 4.1 mg/ml, peanut 1.5 mg/ml, mustard 0.9 mg/ml, poppy seed 5.3 mg/ml, sesame seed 1.5 mg/ml, sunflower seed 3.4 mg/ml. IgE antibody in serum against all extracts but birch pollen, hazelnut and peanut (that were subsequently used in inhibition studies as well as in immunoblot analysis), was assessed by ELISA (4). Results were expressed as optical density (OD). A pool of normal sera was used as negative control.

In ELISA inhibition experiments, the boy's IgE reactivity to Brazil nut was measured after preabsorption for 3 h of

60 µl serum with 60 µl of hazelnut, birch pollen, or peanut extract.

Finally, the patient's IgE reactivity to both Brazil nut and birch pollen was assessed by immunoblot analysis. An immunoblot inhibition experiment was carried out also, using Brazil nut extract as inhibitor and birch pollen as solid phase antigen. Electrophoresis was carried out as previously described (4). Patient's serum showed a marked IgE antibody reactivity to Brazil nut (OD 4000; normal control OD 268), but no reactivity to mustard, poppy seed, sesame seed, or sunflower seed (OD 411-791; normal control OD 447-694).

In ELISA inhibition experiments, absorption of the patient's serum with birch pollen, hazelnut, or peanut extracts did not reduce IgE antibody reactivity to Brazil nut. SDS-PAGE and immunoblot results are shown in Fig. 1. The patient's serum reacted strongly to four distinct Brazil nut proteins at about 18, 25, 33, and 45 kDa, but no reactivity against 2S albumin (10 kDa) was found.

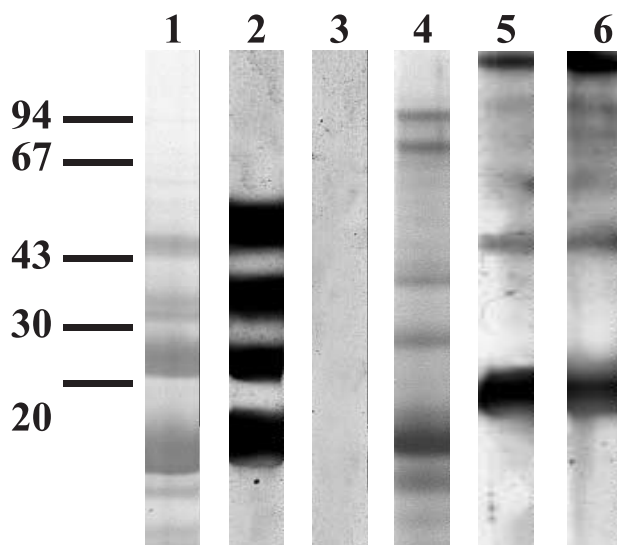


Figure 1. Lane 1: SDS-PAGE electrophoresis of Brazil nut extract; lane 2: the patient's IgE reactivity to Brazil nut; lane 3: IgE reactivity to Brazil nut of a pool of normal sera; lane 4: SDS-PAGE electrophoresis of birch pollen extract; lane 5: the patient's IgE reactivity to birch pollen; lane 6: IgE reactivity to birch pollen by patient's serum pre-absorbed with Brazil nut extract.

With the exception of Ber e 1 reactivity, the allergenic profile was quite similar to that observed in patients in a previous study on Brazil nut allergy (3). Pre-absorption of patients' serum with Brazil nut did not modify the birch-pollen immunoblot profile. Our results suggest that our patient had primary sensitization to Brazil nut, and that allergens other than the seed storage proteins in Brazil nuts may have a clinical role in allergic subjects.

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Anaphylaxis to human seminal plasma

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Key words: anaphylaxis; human seminal plasma; skin prick test.

Post-coital anaphylaxis is a rarely diagnosed disease that is most often caused

by IgE-mediated sensitization to human seminal plasma (HSP) allergens (1,2).

We report the case of a 35-year-old married woman, who had a right oophorectomy at the age of 23 years and a left segmentectomy at the age of 26 years, and had been treated with hormone replacement therapy for infertility since she was 23-years-old. She first experienced episodes of rhinorrhea, cough, generalized urticaria, angioedema of the face and lips, and dyspnea after sexual intercourse with her husband in December 1998. At that time, she was diagnosed as having cryptogenic urticaria after examination by a physician. She had never experienced any urticaria or IgE-mediated disease until December. On 16 May 1999, she had severe anaphylactic symptoms after sexual intercourse again and required emergency room treatment for generalized urticaria, dyspnea, cyanosis, and hypotension. She came to our dermatological clinic the next day for a work up of these symptoms. Although she had taken ethinylestradiol and norgestrel for hormone replacement therapy, the symptoms did not occur after she took this medication, suggesting that this was not the cause.

Laboratory data were all within normal limits. We could not perform human seminal plasma-specific IgE antibody by RAST because the test was not available to us. One week after the anaphylactic reaction, testing for an allergic reaction to her husband's seminal plasma were performed, after obtaining the patient's informed consent. First local application on her skin of the seminal plasma was negative at a 15-minute-reading. Then, the seminal plasma was diluted with physiological saline (Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan) and used for a skin prick test (SPT). Using prick lancet (EWO CARE AB, Sweden) with 1 mm-shoulders to prevent deeper penetration, we carried out SPTs with test solutions. In SPT, a positive reaction to the seminal plasma was observed with a dilution of 10⁻¹. We used the physiological saline as a negative control and 10 mg of histamine chloride (Wako Pure Chemical Industries, Ltd, Osaka, Japan) in 1 ml of the physiological saline as a positive

Repeated IgE-mediated allergic shocks.

control. The test is read after 15 min, and a wheal with a size of half that caused by histamine dihydrochloride (10 mg/ml) or larger is regarded as a positive reaction (1). She showed a negative reaction to the physiological saline. We did not perform SPT with the seminal plasma on normal controls because of ethical problems for fear of sensitization or infection.

We thought that her positive SPT reaction to her husband's seminal plasma was allergic. She was diagnosed as having HSP anaphylaxis. SPT with elements of a condom, diluted with the physiological saline, was performed to look for a latex allergy. She did not react to the condom extract. We educated the patient that her partner should always use a condom during sexual intercourse, and since then she has never experienced any symptoms.

The nature of the human seminal plasma allergens is still unknown, but several protein fractions, which have widely ranging molecular weights from 12 000 to 75 000 Dalton, have been suggested as the possible allergens of human seminal plasma (2). The causative antigens seem to reside in a glycoprotein fraction of human seminal plasma, because the allergenicity of the human seminal plasma is not changed by vasectomy (3). The diagnosis of human seminal plasma anaphylaxis can be established by existence of human seminal plasma-specific IgE measured by RAST, ELISA, or IgE immunoblot (2,3). However, it is suggested that a SPT with human seminal plasma of the partner may be a fast and sensitive diagnostic procedure.

We also consider it very important for patients with human seminal plasma anaphylaxis to always have medications for the emergency treatment of anaphylaxis immediately available.

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Reproducibility of APT

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Key words: AEDS; atopic dermatitis; atopy patch tests; reproducibility.

Atopy patch tests (APTs) are considered a testing procedure enabling the identification of patients with atopic dermatitis (AD), the IgE associated subgroup of the Atopic Eczema/Dermatitis Syndrome AEDS (1) reacting with an eczematous reaction to skin contact with allergens. So far, their reproducibility has been poorly investigated (2–4).

In order to check reproducibility of APT reactions, we performed two identical patch test series simultaneously in 30 subjects affected by atopic dermatitis, 15 males and 15 females (mean age $\pm$ SD = 11.9 $\pm$ 9.7 years). The test substances included two commercially available materials, *Dermatophagoides* mix 20% pet. (Allergopharma-Bracco, Italy) and *Alternaria alternata* 2.4% pet.

(Lofarma, Italy), applied on the upper right and the upper left of the back with Large Finn Chambers on Scanpor tape (Epitest, Tuusula, Finland) for 72 h. Reading was performed according to ETFAD (European Task Force on Atopic Dermatitis) guidelines. The reproducibility of the APT was evaluated by statistical κ calculation (the Choen test).

The percentage of agreement in the frequency of positive and negative responses between the right and the left side was 100%; thus reproducibility proved highly satisfactory both for *Dermatophagoides* mix and *Alternaria alternata* (Table 1). Moreover, when evaluating agreement between the intensity of positive responses to *Dermatophagoides* among patients reacting to it, we found that reproducibility was satisfactory ($k = 0.80$).

In conclusion, *Dermatophagoides* and *Alternaria alternata* APTs may be considered sufficiently reproducible to be employed during a diagnostic testing procedure.

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Nasal and skin histamine responses in allergic rhinitis

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Key words: allergic rhinitis; histamine nasal reactivity; histamine skin sensitivity.

The realization that there are systemic cellular and molecular events that shape various allergic diseases has intensified interest in understanding the relationship between local target organ inflammatory events and associated systemic responses (1). Nasal histamine reactivity has been reported to be associated with development of allergen

skin response in allergic rhinitis (2). The allergen skin response is associated with histamine skin response (3). Thus, our aim was to study whether a relationship exists between nasal and skin responses to histamine in allergic rhinitis.

We studied 22 patients with persistent allergic rhinitis (4) who had mild to moderate symptoms (14 female, aged 26–67 years), 18 normals with positive skin prick test (4) to one or more aero-allergens (11 female, 26–65 years), and 22 normals without any allergen skin response (14 female, 26–63 years). The study was approved by the Hospital Medical Ethics Committee, and informed

Nasal histamine sensitivity was related to skin histamine sensitivity in allergic rhinitis.

Table 1. Reproducibility of atopy patch tests in 30 AD patients

Allergen	Right + /left +	Right – /left –	Right + /left –	Right – /left +	Percentage agreement	k^*
<i>Dermatophagoides</i> mix	20	10	0	0	100	1
<i>Alternaria alternata</i>	1	29	0	0	100	1

* k : <0.20, unsatisfactory; 0.21–0.40, barely satisfactory; 0.41–0.60, fairly satisfactory; 0.61–0.80, satisfactory; 0.81–1, highly satisfactory.

consent was given by all subjects. Nasal histamine challenge tests were performed according to the methods of Simola and Malmberg (2), with some modifications. The challenge was performed stepwise with control solution and doubling concentrations of histamine diphosphate solutions (0.25–16 mg/ml; Sigma Chemical Co., St. Louis, USA). Total nasal symptom scores were assessed after each step. The symptoms included nasal stuffiness (scored none = 0, unilateral = 1, bilateral = 2), rhinorrhea (none = 0, mild = 1, runny = 2), sneezing (none = 0, 1–3 sneezes = 1, > 3 sneezes or consecutive = 2), and nasal itchiness (none = 0, only nose = 1, nose and throat or eye = 2). The test was stopped if total nasal symptom scores increased 4 points or more from control or if the highest concentration of histamine was administered. Immediately, skin prick tests with different concentrations of histamine (5, 10, 50, and 100 mg/ml) were performed on the volar surface of the forearm. Each wheal area was analysed after 10 min and expressed as square mm. We found in random duplicate tests in 15 normal individuals that there was 9% variation in wheal areas. Absolute changes in nasal symptoms score from control were plotted against log-concentrations of histamine, and nasal symptoms score/histamine slope, representing nasal histamine sensitivity, was calculated by linear regression analysis. Similarly, wheal areas were plotted against log-concentrations of histamine, and wheal areas/histamine slope, representing skin histamine sensitivity, was calculated. The slope values were log transformed and results were expressed as mean $\pm$ SEM. Statistical analysis was done using a post hoc Scheffe's test and Pearson's correlation ($P < 0.05$ significant).

Nasal log-slope was significantly higher in patients with allergic rhinitis (0.32 ± 0.06) than in allergen skin test negative normals (0.09 ± 0.05 , $P < 0.05$), with allergen skin test positive normals (0.17 ± 0.07) presenting an intermediate value. Skin wheal areas at 5 and 10 mg/ml in patients with allergic rhinitis were significantly greater than in allergen skin test negative normals ($P < 0.05$, respectively), with allergen skin test positive normals presenting intermediate values. Wheal areas at 50

and 100 mg/ml did not differ significantly among the three groups ($P > 0.05$, respectively). There was no difference in skin log-slope among patients with allergic rhinitis (1.56 ± 0.06), allergen skin test positive normals (1.57 ± 0.07), and allergen skin test negative normals (1.56 ± 0.05). In patients with allergic rhinitis, nasal log-slope significantly correlated with skin log-slope ($r = 0.47$, $P < 0.05$), whereas no relation was found in allergen skin test positive normals ($r = 0.01$, $P > 0.05$) or allergen skin test negative normals ($r = 0.18$, $P > 0.05$).

Our study demonstrated that nasal histamine sensitivity was related to skin histamine sensitivity in patients with allergic rhinitis, suggesting that allergic inflammation generated at the level of the nasal mucosa may affect the skin responsiveness to histamine. Histamine produces a triple response of nerves in the skin and causes an analogous pattern in the nose. During a nasal allergic reaction, histamine stimulates sensory nerves to release substance P (5) and produces neurogenic inflammation. A similar phenomenon is likely to occur in the skin of patients with allergic rhinitis, which may be supported by a study (6) showing that skin sensitivity to substance P is increased in allergic asthma. Many other factors might also contribute to the relationship: H_1 -receptor sensitivity, H_1 -induced production of vasodilators or other mediators, and action of histamine-releasing factors. Our finding may support the evidence that associates allergic rhinitis with systemic inflammatory processes.

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Allergy to tiger nut

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Key words: *Cyperus esculentus*; food allergy; tiger nut; tiger nut milk.

Tiger nut or earth almond ("chufa") (*Cyperus esculentus*) is a tuber belonging to the Cyperaceae family. It is exclusively grown in Valencia (Spain). Its use is very common in Spain, and it is generally employed to obtain a cool drink called tiger nut milk ("horchata") which has a creamy and milky appearance. This drink is obtained by macerating tiger nuts with water and sugar, and it is widely consumed in Spain.

Raw tiger nut can be eaten too. In spite of the widespread

IgE-mediated oral allergy.

consumption of tiger nuts in some areas, tiger nut allergy has rarely been reported. Here we described two cases of IgE-mediated tiger nut allergy.

Patient 1: a 43-year-old-woman, with seasonal rhinoconjunctivitis and bronchial asthma from hypersensitivity to pollen (grass, *Olea*, *Artemisia*, *Chenopodium*, *Salsola* and *Plantago*) reported oral pruritus and bronchospasm immediately after drinking tiger nut milk. She became asymptomatic after treatment with antihistamines and corticosteroids in 2–3 h. She also reported oral pruritus and conjunctivitis after eating apple, pear, peach, melon and coconut. Total IgE was 204 kU/l. Specific IgE (CAP Pharmacia) was positive to *Olea* (5.7 kU/l), *Salsola* (8.3), *Plantago* (1.9), *Lolium* (0.6), *Artemisia* (0.4), and rBet v 2 (1.6). Specific IgE to melon, pear, peach, and coconut was negative. Specific IgE to tiger nut extract was carried out by RAST (Pharmacia Phadebas RAST) with a positive result (0.6 kU/l). Prick-tests with common inhalants and latex were positive with pollen from *Olea*, grass, *Artemisia*, *Plantago*, *Chenopodium* and *Salsola*. Prick-test with commercial extracts and prick by prick were negative to melon, pear, apple, peach, and coconut. We performed prick-tests with tiger nut and tiger nut milk with the following results: histamine 10 mg/ml (8 × 7 mm of wheal), tiger nut milk as is (4 × 3), tiger nut extract 5% w/v ALK-Abelló (7 × 4), prick by prick with dampened tiger nut (8 × 6). SDS-PAGE immunoblotting with tiger nut extract showed a IgE-binding protein of 25 kDa.

Patient 2: an 11-year-old boy, with seasonal rhinoconjunctivitis and bronchial asthma from hypersensitivity to pollen (grass, *Olea*, *Chenopodium*, *Salsola* and *Plantago*) reported oral pruritus with tongue and lips angioedema immediately after eating raw tiger nut. He became asymptomatic without treatment after 2–3 h. He suffered a similar episode after eating a banana. Total IgE was 85.7 kU/l. Specific IgE (CAP Pharmacia) was positive to *Olea* (2.5 kU/l), *Salsola* (2.9), *Lolium* (0.4) and negative to banana. Specific IgE to tiger nut extract (Pharmacia Phadebas RAST) was positive (1 kU/l). Prick-tests with common inhalants and latex were positive to pollen from *Olea*, grass, *Artemisia*,

Plantago, *Chenopodium* and *Salsola*. We performed skin tests (prick-by-prick) with banana (4 × 5 mm of wheal) and dampened tiger nut (3 × 3). Histamine at 10 mg/ml developed a 3 × 3 mm wheal. SDS-PAGE immunoblotting with tiger nut extract showed a IgE-binding proteins of 37.45 (main band), 70 and > 100 kDa.

Prick-tests with tiger nut extract (5% w/v) and tiger nut milk were negative in 40 controls (20 of them suffering hypersensitivity to pollens).

In spite of its popular consumption in Spain, both as raw tiger nut and tiger nut milk, tiger nut (*Cyperus esculentus*) hypersensitivity is very rare. An occupational hypersensitivity pneumonitis has been described in a patient working in a tiger nut milk factory (1). IgE-mediated hypersensitivity has been previously reported in only four patients: two cases of anaphylaxis (2,3), one case of oral allergy (4) and one case of urticaria (3). Here we described two patients suffering from IgE-mediated tiger nut allergy. Patient 1 developed oral allergy and bronchospasm after drinking tiger nut milk and patient 2 suffered tongue and lips angioedema after eating raw tiger nut. Prick-tests with tiger nut and tiger nut milk have been demonstrated to be useful in our patients, as in patients described above. Furthermore, hypersensitivity to pollen and other vegetable foods is common in this group of patients.

IgE-binding protein bands in tiger nut immunoblottings are variable. In patient 1, we identified an IgE-binding protein band of 25 kDa. In patient 2, we found IgE-binding protein bands of 37.45 (mainly), 70 and > 100 kDa. Previously, two IgE-binding proteins of 17.7 and 64 kDa had been identified in a patient with an oral allergy to tiger nut (4). Moreover, IgE-binding to proteins of 16 and 25 kDa was described in a patient with urticaria due to tiger nut (3).

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Casein, an important house dust allergen

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Key words: casein; house dust; indoor allergen; milk; mite; pet; plaster.

The use of casein and gelatine (bone glue dust) in indoor plasters is not commonly known. In Finland, casein has been used since the 1960s to improve the handling properties of plaster. We measured casein in 91 house dust samples and compared the level to better known indoor allergens. Casein, cat (*Fel d 1*), dog (*Can f 1*) and mite (*Der p 1*, *Der f 1*) allergens were measured with the ELISA method (1).

Casein was detected in all but one dust sample. The median casein level was 30 µg/g (range 4–3300 µg/g), which was higher than those of pet animals and mites; cat 0.11 µg/g (range 0.01–1072 µg/g), dog 0.76 µg/g (range 0.01–2365 µg/g), *Der p 1* < 0.01 µg/g (range < 0.01–366 µg/g)

House dust contains more milk casein than pet and mite allergens

and *Der f 1* < 0.01 µg/g (range < 0.01–15 µg/g). In 27 pure plasters the median casein content was 2.4 µg/g (range < 0.1–8300 µg/g). The highest level was in a floor plaster.

In this study, casein was measured in the settled dust. It is not known whether casein is airborne. Further, it is not known how commonly organic proteins are used in indoor construction materials. At least casein and egg proteins may be used in organic paints. Indoor casein may also be derived from food. However, high casein levels were detected in dusts from places where milk was not used (360 µg/g) or not allowed (laboratory office, 655 µg/g). In addition, casein was also high in dusts where no whey protein could be demonstrated.

Several manufacturers in Finland have changed from casein to synthetic materials in the 1990s. However, many houses still contain casein. Since 1982, casein has not been allowed in plasters in Sweden. It is difficult to estimate how much casein or gelatine-like compound containing surfaces still exist in housing stocks worldwide. One Dutch study exists in which a whey protein (β-lactoglobulin) was detected in house dust (2).

The added casein in a plaster is not easily recognized, because casein is not listed on the safety data sheet, since it is not considered harmful for health. However, death has been described after inhalation of milk proteins (3). Casein has also been used in latex gloves and allergic reactions have been described after skin contact to milk proteins (4).

In Nordic countries, pet dander is one of the most common indoor sensitizers, whereas mites are not considered important (5). In this study, casein was shown to be an abundant indoor allergen exceeding the more well-known animal and mite allergens. It should be considered whether airborne food allergens play a role in immediate skin allergy or in delayed-type food allergy and atopic eczema, especially in small children crawling in close contact to house dust potentially containing casein.

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Celecoxib, safe in NSAID intolerance

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Key words: celecoxib; hypersensitivity; NSAID.

URTICARIA AND/OR ANGIOEDEMA (U/AE) following the ingestion of nonsteroidal antiinflammatory drugs (NSAIDs) is a common occurrence in clinical practice (1). An alternative therapy is needed for relief of pain and inflammation in these people.

The aim of this study is to determinate the tolerance of celecoxib (a high affinity COX-2 inhibitor) in 20 patients suffering U/AE associated with NSAIDs.

All 20 patients tolerated celecoxib.

Patients were aged from 23 to 72 years, and were of either sex. Each had to have experienced two or more separate documented episodes of U/AE following ingestion of at least two different NSAIDs. The diagnosis was based on a detailed history and confirmed by an oral challenge with the suspected drugs in some cases.

The following exclusion criteria were used: history of sulfonamide allergy, β-blocker treatment, pregnancy or lactation, lactose intolerance, chronic urticaria, contraindication to epinephrine, and those considered to be “difficult collaborators.”

Provocation tests were carried out in a single blind manner. The oral challenge protocol consisted of oral administration of celecoxib with increasing doses given at 60 min intervals. During the challenge procedure, blood pressure, pulse and cutaneous symptoms were monitored. All patients remained in hospital under medical supervision for 3 h after each drug-dose challenge. Informed consent was obtained for every patient submitted to oral provocation testing with celecoxib.

On day 1, patients underwent complete history and physical examination, with measurement of blood pressure, pulse rate, and cutaneous examination. If these results were normal, the patients underwent placebo (lactose) challenge. Patients were examined 1 h later. If all measurements were normal, 50 mg of celecoxib was administered, and the patients remained under medical supervision in the hospital for 3 h.

On day 2, clinical supervision measures were repeated (48 h later). Another oral challenge was performed with higher doses of celecoxib (100 mg). If no reaction was observed 1 h later, a 200 mg dose was given.

On day 3, if no adverse reaction was observed, 200 mg of celecoxib was given again to each patient, 7 days after the onset of the challenge procedure.

Table 1. Epidemiological data, drugs, and clinical findings of NSAID hypersensitivity

Patients	Sex (M/F)	Age	POC	Symptoms associated with NSAID intake	Implicated drugs	OC celecoxib (200 mg)
1	M	31	ASA +	U/AE	ASA, dipyrone	Negative
2	F	31	–	AE	ASA, dipyrone, ibuprofen	Negative
3	M	54	ASA +	AE	ASA, ibuprofen	Negative
4	M	60	–	U	ASA, dipyrone, propyfenazone	Negative
5	F	56	–	U	ASA, dipyrone	Negative
6	F	53	–	U/AE	ASA, piroxicam	Negative
7	F	72	–	AE	ASA, dipyrone	Negative
8	M	46	–	AE	ASA, dipyrone, ibuprofen	Negative
9	F	39	ASA +	U/AE	ASA, ibuprofen	Negative
10	M	33	–	AE	ASA, dipyrone	Negative
11	F	24	–	U	ASA, clonixin	Negative
12	F	23	ASA +	U	ASA, ibuprofen	Negative
13	M	63	–	U/AE	ASA, dipyrone, indomethacin	Negative
14	F	25	Dipyrone	U	ASA, dipyrone	Negative
15	F	62	–	U/AE	ASA, ibuprofen	Negative
16	M	28	–	U	ASA, dipyrone, clonixin	Negative
17	F	59	ASA +	AE	ASA, dipyrone	Negative
18	F	68	–	AE	ASA, propyphenozone	Negative
19	M	49	–	U	ASA, indomethacin	Negative
20	M	31	ASA +	U/AE	ASA, acetaminophen, ibuprofen	Negative

AE: angioedema; ASA: acetylsalicylic acid; OC: oral challenge; POC: previous oral challenge; U: urticaria; U/AE: urticaria and/or angioedema.

The challenge test was accepted as positive if one of the following symptoms appeared: a cutaneous reactions such as erythema, urticaria and/or angioedema, or laryngeal edema.

Epidemiological data, the drugs involved, and clinical findings of NSAID hypersensitivity are shown in Table 1. At the end of the challenge procedure, all 20 participants tolerated the celecoxib dosage of 200 mg. Adverse reactions were observed in no patients.

Celecoxib is a novel COX-2 inhibitor with a biochemical and pharmacological profile clearly distinct from that of current NSAIDs.

In our study we observed that celecoxib, a highly selective inhibitor of COX-2, did not cause U/AE in people suffering from NSAID hypersensitivity.

Celecoxib seems to be a safe drug for this group. These findings indicate that celecoxib may be useful in the treatment of pain and inflammation for such people (2). The results also seem to confirm the cyclooxygenase theory (3).

Nevertheless, further challenges with celecoxib, and other new highly selective COX-2 inhibitors, on a larger series of patients are needed to determinate its real safety in people with U/AE associated with NSAID hypersensitivity.

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Systemic contact dermatitis to gentamicin

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Key words: aminoglycosides; drug allergy; cross-reactions; gentamicin; patch test; systemic contact dermatitis.

Sensitization and contact dermatitis to drug-containing creams are well known and sometimes spread of this eczematous eruption may develop. However, eczematous eruption as a first manifestation of systemic drug allergy is uncommon (1).

An otherwise healthy 30-year-old woman developed a

generalized eczematous eruption 24 h after a cesarean section. Bupivacaine, lidocaine, ampicillin 1 g IV q6 h, gentamicin 80 mg IV q8 h, ketorolac 30 mg IV q6 h, pethidine 100 mg IV and met-amizole magnesium 2 g IV prn were administered. After the eczema developed, ampicillin and gentamicin were discontinued and, as 36 h later the eruption persisted, all the drugs were withdrawn. Prednisone 30 mg PO daily and chlorpheniramine 6 mg PO q8 h were started and the patient's dermatitis improved over the next two weeks.

A generalized eczema developed 24 hrs after drug administration.

Patch tests with the GEIDC (Spanish Investigation Group in Contact Dermatitis) standard series were negative. Skin prick test with latex was negative. Skin prick test, intradermo-reactions and provocation tests with lidocaine and bupivacaine were negative. Provocation tests with pethidine, ampicillin, metamizole magnesium and ketorolac were also negative. Skin prick test and intradermo-reaction with gentamicin 1 mg/ml were negative; and thus, a systemic challenge test with gentamicin 80 mg was carried out the same day. Six hours later, the patient developed a red pruritic lesion at the injection site of the parenteral administration. Twenty-four hours later she presented axillary eczema and an intradermo-reaction flare-up. Patch test with gentamicin, neomycin, amikacin, tobramycin (all at 20%) and streptomycin (1%), all in petrolatum, were performed, proving positive for gentamicin, neomycin and amikacin. A skin biopsy from the gentamicin patch test site showed an inflammatory reaction of papillary bodies and superficial venous plexus with lymphocytic infiltrates consistent with acute contact dermatitis. Immunofluorescence was negative.

Once the study was completed, the patient recalled a previous contact with a gentamicin ointment with no adverse reactions.

Systemic contact dermatitis occurs following oral or parenteral administration of an allergen in subjects who had previously been sensitized from a local administration. In these cases, patch tests are of value in identifying the drug responsible. Testing with drugs with a similar chemical structure may also be of importance in the work-up study of cross-reactions (1). Cross-reactions between aminoglycoside antibiotics have long been known (2–5). Aminoglycoside antibiotics may be divided into two groups depending on the aminocyclitol nucleus: streptidine (streptomycin) and deoxystreptamine (neomycin, kanamycin, gentamicin, paramomycin, spectinomycin and tobramycin). Another antigenic determinant is neosamine, a diamino sugar present in neomycin and, with minor changes, also in paramomycin, kanamycin, tobramycin, amikacin and isepamicin (5). Streptomycin shares

no common antigenic structures with the other aminoglycoside antibiotics and cross-sensitivity with streptomycin has not been reported.

Although most cases of contact dermatitis from gentamicin arise from cross-sensitivity to neomycin, the patient described here appears to have been sensitized originally to gentamicin.

This case not only presents a rare manifestation of systemic drug allergy, but also emphasizes the safety and usefulness of patch tests in the diagnostic work-up of non-immediate cutaneous allergic drug reactions, particularly when more than one drug is involved.

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Anaphylaxis to streptomycin

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Key words: streptomycin; IgE-mediated allergy; skin tests.

FEW ANAPHYLACTIC REACTIONS provoked by streptomycin subtherapeutic doses have been reported (1–4). Such doses were either present in contaminated

food (1) or added to cell culture media and administered during *in vitro* fertilization (2,4) or during immunotherapy with phytohemagglutinin-lymphokine-activated killer cells (3). In most of these reactions an IgE-mediated pathogenic mechanism was demonstrated on the basis of skin-test positivity (1,2,4).

We describe an anaphylactic reaction caused by streptomycin absorbed through the hand skin lesions of a subject affected by an allergic contact dermatitis.

We studied a 59-year-old farmer, with a 10-year history of chronic hand eczema due to a previously diagnosed delayed hypersensitivity to thiurams, who had had an anaphylactic shock following an accidental contact with streptomycin. While he was giving an injection to a cow, he accidentally spilled some streptomycin solution on his hand. Immediately afterwards he developed angioedema of the hand and, in a few minutes, generalized urticaria and angioedema with dyspnoea, dizziness, and severe hypotension. After treatment with intramuscular epinephrine, and intravenous 6-methyl-prednisolone and chlorphenamine, symptoms resolved completely in 10 h.

Six years later, we skin-prick-tested the patient with streptomycin at a concentration of 1 mg/ml in 0.9% NaCl, inducing a positive reaction (13 × 15 mm wheal with pseudopodiae) after 10 min, when the patient also exhibited face erythema and angioedema as well as conjunctivitis. He was immediately treated with clorphenamine maleate and

Unusual case of sensitization by cutaneous absorption

methylprednisolone intravenously; 90 min later the symptoms regressed.

Prick and intradermal histamine tests produced wheals with maximum diameters of 7 and 12 mm, respectively. Prick and intradermal tests with streptomycin at a concentration of 1 mg/ml were negative in 20 healthy control subjects, five of whom had previously tolerated this antibiotic.

The assay (UniCAP® Specific IgE; Pharmacia & Upjohn, Uppsala, Sweden) for specific IgE to streptomycin was negative (<0.35 kU/l).

Patch tests with the European Standard Series (Bracco Industria Chimica, Milan, Italy) confirmed the thiuram positivity (++).

The clinical findings and the positive prick test with streptomycin, as well as the systemic reaction after testing, strongly suggest that the patient had developed an IgE-mediated allergy to this drug.

We could not show specific IgE by the RAST technique. It should be considered, however, that we used an experimental prototype.

The way in which our patient was exposed to streptomycin was unusual. However, although rare, anaphylaxis has also been reported after topical administration of other aminoglycosides such as bacitracin (5). All such patients, including ours, had applied the drug to a compromised skin barrier. Thus, ready access to the systemic circulation seems to be a prerequisite for the development of these cases of anaphylaxis. Thiuram hypersensitivity had caused the hand excoriated dermatitis of our patient, who was routinely exposed to contact with articles made of rubber such as milking equipment and tubes.

Taking into consideration the fact that he had never been administered streptomycin and had suffered from hand eczema for 10 years, he could have been previously sensitized by cutaneous absorption while administering antibiotics to the cows.

The systemic reaction after prick testing suggests a more cautious approach in evaluating anaphylactic reactions to streptomycin, starting with concentrations of 0.1–1 ng/ml as others have done (4) and, in case of negative results, gradually reaching the concen-

tration of 20 mg/ml used by Tinkelman et al. (1).

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A new pollen – fruit cross-reactivity

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Key words: *Chenopodium* pollen; banana; melon; peach; allergen cross-reactivity.

CHENOPODIACEAE ARE WEEDS widely spread in cultivated lands. In our zone (Valladolid, Spain), *Chenopodium album* is a plentiful weed, what is usually found

in the beet-cultivated lands. To eat certain fruits and vegetables may elicit allergic symptoms localized to the

oral mucosa in sensitized subjects, giving rise to the so-called oral allergy syndrome (OAS). We have found several cases of patients with pollen allergy and positive skin prick test (SPT) to *Chenopodium album*-pollen, who showed OAS after eating fresh fruits: banana, melon and peach. Sera from 9 patients with *Chenopodium*-pollen allergy were used. Five of them also referred OAS in relation to eating several fruits, more often banana, melon and peach. All these patients had SPT positive to *Chenopodium*-pollen extract (ALK-Abelló, Madrid, Spain) greater than 3 mm in diameter, and exhibiting RAST levels of 2.63–13.48 kU/l by the CAP System (Pharmacia, Uppsala, Sweden). Prick by prick with fresh fruits was done for the 5 patients who had symptoms eating fresh fruits above mentioned, according to the method of Dreborg and Foucard (1). Protein concentration (6.63 mg/ml; 50% glycerine) was determined by the method of Lowry et al. (2). Extracts of banana, melon, pulp and peel peach, were prepared by us only for this *in vitro* study. Analytic electrophoresis was performed in 16% polyacrylamide gels in the presence of SDS, as previously described (3).

Immunoblot assays were performed for the 9 patients with *Chenopodium*-pollen allergy. At least, 6 allergenic bands could be identified, ranging from molecular weight (MW) of 10–20 kDa. A component with MW of 14 kDa was detectable in 6 of patients, and acts as a major allergen. Specific IgE detection to *Chenopodium* was not observed in any of the 8 sera used as control.

Inhibition assays were carried out for 6 hypersensitive patients to one or more of the fruit allergens (Fig. 1). *Chenopodium*-pollen blot was inhibited with the following extracts: *Chenopodium* (positive control of inhibition), *Anisakis simplex* (used as an irrelevant control), peach (peel and pulp), banana and melon. All these patients showed a complete inhibition of the *Chenopodium* extract by banana. Inhibition by melon extract was

Allergen similarities of *Chenopodium* and banana, melon and peach

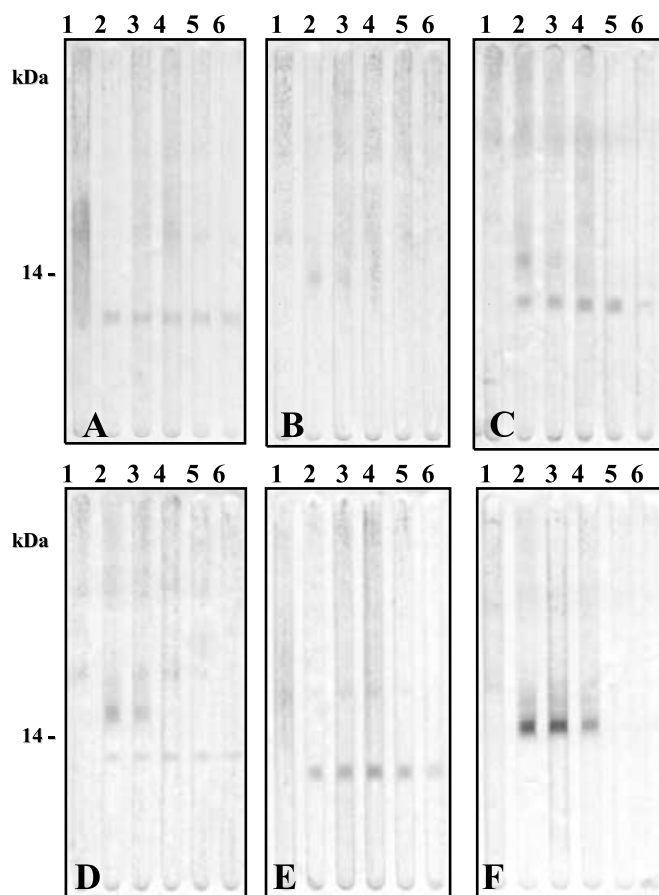


Figure 1. Inhibition assays of IgE-binding to *Chenopodium*-pollen extract of sera from 6 patients (A–F) by pollen extract from *Chenopodium* (lane 1), *Anisakis simplex* (lane 2), peel peach (lane 3), pulp peach (lane 4), melon (lane 5) and banana extracts.

complete in three patients and partial in the others three. The pulp and peel peach behaved in different inhibition percentage, and a higher inhibition was obtained with the pulp than with the peel in 4 of the study patients.

In conclusion, by means of blot-inhibition we have demonstrated the existence of cross-reactivity between *Chenopodium*-pollen and banana, melon and/or peach, an observation that what not previously described.

Lately, two major allergens in banana have been isolated, characterized and identified as class I chitinases (4). Lipid-transfer proteins have also got involved as relevant allergens in fruit allergy (apple and peach) (5, 6).

Our preliminary data suggest the necessity of more extensive studies, to elucidate and characterize the molecular structures mainly involved in such cross-reactivity.

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Immunotherapy triggering acute VCD

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Key words: immunotherapy; VCD; vocal cord dysfunction.

Vocal cord dysfunction (VCD) is an involuntary paradoxical adduction of the vocal cords during inspiration and/or expiration that results in upper airway obstruction. It can mimic asthma (1), exercise-induced bronchospasm (2), episodic dyspnea (1), and rarely, anaphylaxis (3). Typical symptoms include stridor, coughing, dyspnea, choking sensation, and dysphonia (1,4). Many triggers for VCD are shared with asthma, including stress, exercise, upper respiratory infections, and inhalation of irritants such as methacholine (5). Other triggers include odors, athletic activity, or the presence of medical personnel in the room (4). To date, immunotherapy has

First case of vocal cord dysfunction on IT.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Air Force, the Department of Defense, or the United States Government.

not been reported as a specific trigger for episodes of acute vocal cord dysfunction.

A 49-year-old female with laryngoscopy-proven VCD (without evidence of underlying asthma) was started on immunotherapy for allergic rhinitis due to failure of medical management. She tolerated her first injection without difficulty. Forty minutes after her second injection (0.1 cc of 1 : 100 000 dilution), however, she developed an acute voice change followed by stridor and dyspnea. She denied any other systemic symptoms. Her vital signs, peak flow, and pulse oximetry were normal. Physical examination was notable only for pronounced dysphonia and inspiratory and expiratory stridor heard over the anterior neck. Spirometry was performed (Fig. 1), which showed normal forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), but significant truncation of the inspiratory limb of the

flow-volume loop consistent with acute vocal cord dysfunction. She was monitored in the clinic and released. Five days later she returned to resume her build-up immunotherapy. At 35 min following her injection, she again developed acute voice change and dyspnea with spirometry identical to her previous episode.

Due to the recurrent nature of her reactions, immunotherapy was electively discontinued.

In conclusion, there are many and varied triggers that have been reported for VCD. To the best of our knowledge, immunotherapy has not been previously identified as a specific precipitant for acute VCD. As VCD has been shown to mimic anaphylaxis, caution is required when starting these patients on immunotherapy. Early recognition of acute VCD can prevent potentially harmful and unnecessary treatments that are commonly seen with misdiagnosis in this condition.

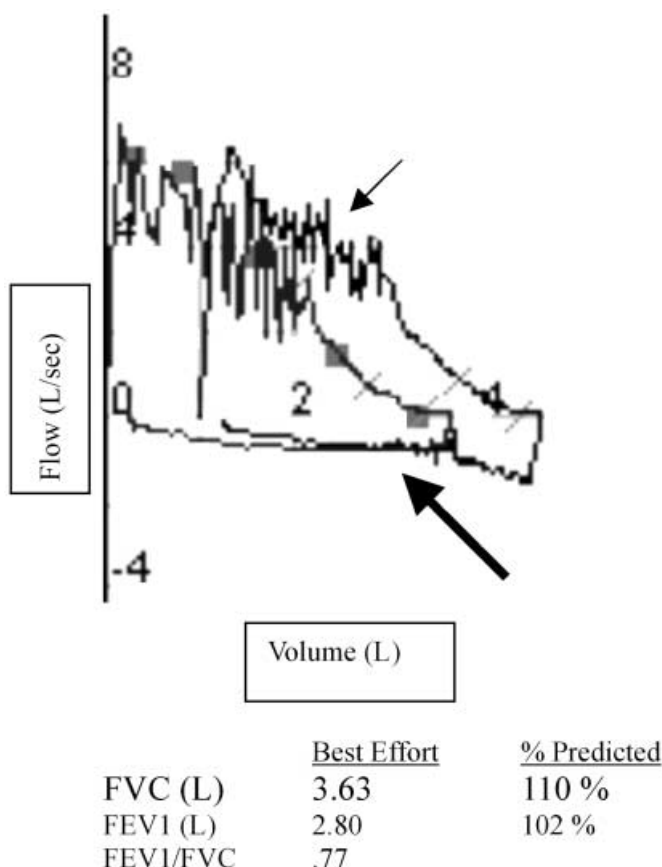


Figure 1. Spirometry including flow-volume loops (two separate maneuvers), demonstrating classic truncation of inspiratory limb seen in VCD (thick arrow). Expiratory involvement is also evident (thin arrow).

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A combination of wheatflour, ethanol and food additives inducing FDEIA

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Key words: anaphylaxis; urticaria; wheat allergy.

WHEAT ALLERGY may present different clinical outcomes including food allergy, baker's asthma or food dependent exercise-induced anaphylaxis (FDEIA) (1). It mainly occurs after ingestion of wheat in childhood and may be lost after a period of strict avoidance (e.g., 1–2 years). By contrast, wheat allergy is rare in adults (2), by whom wheat dependent exercise-

Food dependent exercise-induced anaphylaxis can be complex.

induced anaphylaxis is more often (3,4). The relevant allergens of wheat are heterogeneous. Wheat proteins are classified into three fractions according to their solubility. These fractions include water-soluble albumins, salt-soluble globulins and ethanol-soluble prolamins (gliadins) and the insoluble glutenins (1). Palosuo et al. reported that gluten is the major allergen for IgE-mediated reaction to wheat (3).

Here we report on a patient (female, 48 years) with suspected food-allergy, who complained of urticaria, angioedema, dyspnea and finally unconsciousness after a restaurant meal (deer-roast with sauce). A second episode followed after ingestion of a convenience food product and finally after ingesting mulled wine in combination with wheatflour based pastries. The patient was skin prick tested (SPT) using the following allergens: grass-, birch- and mugwort pollen, cat epithelium, alternaria and house dust mites and the suspected food allergens including wheat flour, rye flour and gluten, in addition total IgE and specific IgE antibody levels were measured. Skin prick test was positive to birch pollen, wheatflour and gluten. Total serum IgE was 131,00 kU/l, IgE antibody levels were CAP-II (2,20 kU/l) for wheatflour, CAP-III (3,97 kU/l) for gluten and CAP-0 (<0,35 kU/l) for birchpollen and grasspollen. According to these results wheat allergy was suspected as a cause of the anaphylactic reactions and the patient received advice to keep a wheat-free diet over 10 days. The diet was followed by a double-blind placebo-controlled food challenge (DBPCFC). The DBPCFC was negative with wheatflour (40 g), gluten (10 g) and food additives (5), given either separately or in combination with exercise (HF > 120/min) or ethanol (30 ml), respectively. Finally we challenged additively, ethanol, wheatflour and exercise in combination. Then a positive reaction (generalized urticaria) was elicited and antiallergic intervention was necessary (150 mg prednisolon and 4 mg fenistil i.v.) consecutively.

The present case demonstrates that many different factors may aggravate the elicitation of an anaphylactic reaction in a wheat sensitive individual. Our observation is comparable to a case reported by Aihara Y et al. (6) in which a patient with FDEIA reacted only after the simultaneous intake of wheat and umeboshi. In a

review of 163 cases of FDEIA, wheat was found to be the most frequently aggravating factor for FDEIA (4). Taken together this case demonstrates patients suffering from FDEIA need a detailed allergic work up including DBPCFC with several possible eliciting factors, such as food additives, ethanol and exercise.

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IgE-mediated anaphylaxis to sheep's and goat's milk

M. J. Alvarez*, M. Lombardero

Key words: IgE-mediated food allergy, IgE-mediated anaphylaxis, casein allergens, goat's milk allergy, sheep's milk allergy, immunoblotting.

IgE-mediated food allergies encompass symptoms ranging from mild discomfort to life-threatening anaphylaxis. The difficulty in identifying the allergen

and the small quantities of hidden allergens (wheat, milk, soy) that may

This nonatopic man tolerate cow's milk, however.

contain processed foods makes allergen avoidance troublesome. We report a 43-year-old nonatopic man presenting anaphylactic reactions following the ingestion of several foods (white coffee, croquettes, chocolates and cheese-containing groceries). He tolerated cow's milk, dairy products and meat. Skin prick tests with a battery of food allergens including among others, cow's milk and fractions (casein, α -lactalbumin and β -lactoglobulin) were negative.

Following the ingestion of one sheep-milk curd he presented chest tightness, dyspnea, vomits, abdominal cramps and hypotension. Prick test were positive with sheep's milk (15 × 15 mm), goat's milk (9 × 9 mm) and with the sheep's milk curd (25 × 20 mm). Total-IgE was 6 kU/l and specific-IgE to sheep and goat's milk were 0.62 and 0.60 kU/l. Specific-IgE to cow's milk, casein, α -lactalbumin, β -lactoglobulin and bovine lactoferrin was undetectable. Immunoblotting (1,2) showed IgE-binding bands by 25 kDa and, between 50 and 75 kDa in goat's and sheep's milk lanes (Fig. 1).

IgE-mediated milk allergy is common among infants but it can also develop in adult life being casein the predominant allergen (3). Casein is present in the milk of other species (goat, sheep) with high sequence homologies (4) and, cow's milk allergic children present allergic reactions to goat's milk (5). The IgE-binding band by 25 kDa at sheep and goat's milk lanes could correspond to α or β casein. The other, between 50 and 75 kDa might correspond to both, serum albumin or most likely, since our patient tolerated the ingestion of lamb, to casein aggregates. In keeping with us, a number of reports (6–8) show IgE-mediated allergy to sheep's and goat's cheese in adults and children who tolerated cow's milk.

Milk caseins are often labeled as additives in many manufactured foods

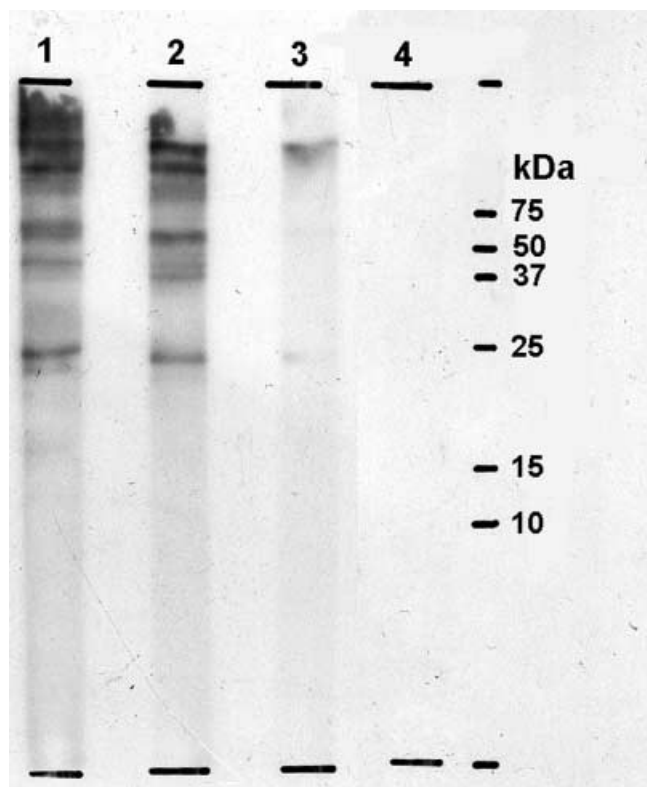


Figure 1. IgE immunoblotting of goat's milk (lane 1), sheep's milk (lane 2) and cow's milk (lane 3). Lanes 4 and 5 correspond to goat's milk incubated with dilution buffer (negative control) and molecular weight markers, respectively.

and the origin of the milk utilized to obtain caseins is unusually addressed. Further, contamination of milk proteins-free products processed on equipment used to dairy-containing foods is possible. Our patient was instructed to avoid goat and sheep's milk, dairy products and all the manufactured foods containing caseins or labeled as "caramel color", "natural flavouring" or, "protein flavour". Following such precautions, he has been symptom-free

despite regularly consuming cow's milk. The need of improving the labeling of manufactured foods to avoid fatal reactions and allow the accurate diagnosis of IgE-mediated food allergy is stressed.

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