

Double sensitization to enzymes in a baker

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Key words: alpha-amylase; bronchial challenge; lysozyme.

THE ENZYMES alpha-amylase and lysozyme have been identified as inhalative allergens in baker's asthma (1-4), and in egg-processing or pharmaceutical workers (5-10), respectively.

We report the case of a 41-year-old man who worked in a bakery for 25 years. After 22 years of glazing rolls with fresh egg, he began to use a spraying device for the egg mixture. A few months later he began to develop rhinoconjunctivitis and asthma just minutes after this activity. He remained asymptomatic during weekends and holidays.

He then worked on mixing wheat flour to make bread. Initially he was free of symptoms, but 9 months later he presented with rhinoconjunctivitis and asthma. He had no symptoms on ingestion of egg or wheat flour. At home, he had seven birds and a cat, but his symptoms did not worsen on exposure to these pets, to house dust, or pollen.

Physical examination, blood cell count, biochemistry, and chest radiographs were all normal. Skin prick test (SPT) with commercially available extracts (Leti, Spain), were positive to egg white, egg yolk, ovomucoid, wheat flour, barley flour, *Dermatophagoides pteronyssinus*, *D. farinae*, *G. fusca*, *L. destructor*, *T. putrescentiae*, and cockroach, as well as to a lysozyme extract (Wassermann) at 10 mg/ml, and to alpha-amylase extract (1 mg/ml). SPT were negative to a bat-

tery of pollen and molds, cat and dog dander, canary and pigeon feathers, ovalbumin, and rye flour.

Total serum IgE was 1142 kU/l. IgE antibodies were detected to egg white (2.07 kU/l), egg yolk (0.86), ovomucoid (2.26), wheat flour (3.21), barley flour (1.95), alpha-amylase (0.39), lysozyme (2.05), *D. pteronyssinus* (5.60), *D. farinae* (5.48), *L. destructor* (3.70) and *T. putrescentiae* (5.58) (CAP Pharmacia, Sweden). The test was negative to ovalbumin, and to canary and pigeon feathers.

Spirometry revealed a forced vital capacity (FVC) of 105%, forced expiratory volume in 1s (FEV₁) of 94%, FEV₁/FVC of 93%, and forced expiratory flow (FEF₂₅₋₇₅) of 64%.

Specific bronchial challenge to lysozyme (tidal breathing method) elicited an early asthmatic response (22% fall in FEV₁ in 10 min). Specific bronchial challenge to alpha-amylase elicited an early asthmatic response with a 24% fall in FEV₁ in 20 min.

We have demonstrated IgE sensitization and clinical sensitivity to two enzymes from different sources by SPT, IgE antibody determination, and bronchial provocation test. The two enzymes are lysozyme (from egg used to decorate rolls) and fungal alpha-amylase (used to improve bread qualities). This patient was also strongly sensitized to dust mites, although no symptoms have yet been produced.

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Allergy to garlic

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Key words: children; garlic; food allergy; urticaria.

Garlic belongs to the Liliaceae family. This family is divided into two sub-

A 16-month-old boy with urticaria and positive SPT.

families, Asparagoidea (asparagus) and Aliolidea (garlic, onion, chive, leek and aloes). Hypersensitivity to garlic has been described as a cause of contact dermatitis and occupational asthma and rhinitis. Immediate allergic reactions to garlic ingestion (1,2) or contact (1) are rare, especially in children.

We report a case of IgE-mediated urticaria after contact and ingestion of raw garlic in a child.

A 16-month-old boy with a personal history of cow's milk and egg-white allergy, developed urticaria on the face and neck immediately after local contact with raw garlic. From the age of 12 months he had ingested cooked garlic with tolerance. He had ingested onion from the age of 6 months with no symptoms.

Skin prick and prick-prick tests were positive with commercial garlic extract (Stallergènes) and fresh raw garlic with a wheal diameter of 15 × 9 mm and 17 × 8 mm, respectively. The prick-prick test was negative with fresh cooked garlic. Skin prick and prick-prick tests were negative with both commercial onion extract (Stallergènes) and fresh raw and cooked onion. We also tested 10 children, followed in our Immunoallergy Department, with fresh raw and cooked garlic and onion, as controls, all being negative. Specific IgE to garlic and onion (Pharmacia CAP System) were negative (< 0.35 kU/l).

Contact challenge was positive (urticaria) with raw garlic and negative with cooked garlic. Oral challenge with raw garlic was positive with generalized urticaria within 10 min after ingestion. Oral challenge with cooked garlic was negative.

The child is on raw and cooked garlic eviction, being asymptomatic.

The immunoblotting analysis (Ala-BLOT DPC-Amerlab) showed two proteinic bands with molecular masses of approximately 12 kDa and around 40–50 kDa, probably corresponding to the previously identified garlic proteins mannose-binding lectin (3) and alliinase (4), respectively.

Pérez-Pimiento et al. (5) also identified a band with a molecular mass of 12 kDa

to young garlic, garlic, onion and leek extracts in a woman allergic to young garlic. Asero et al. (1) also found bands with molecular mass of 10, 20 and 40 kDa in a woman with urticaria after ingestion and contact with raw and cooked garlic.

We found no cross-reactivity between onion and garlic, two foods that belong to the same family. Asero et al. (1) also reported a case without cross-reactivity between these foods. However, some authors found immunological cross-reactivity between the Liliaceae family (6,7). Probably the level of cross-reactivity among the different Liliaceae vegetables varies among individuals.

Since our child tolerated cooked garlic, we suggest that the allergenic fraction to which he is sensitized is denatured by heat treatment. Nevertheless, a case of systemic urticaria associated with ingestion of both raw and cooked garlic has been described by Asero et al. (1). Probably this patient had a garlic allergy caused by heat-resistant allergens.

By allowing cooked garlic in the child's diet, we might delay complete immunological tolerance to garlic proteins. Or might the consumption of cooked garlic even favour acquisition of complete oral tolerance and recovery from garlic allergy? More data will be necessary to answer this question.

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Eotaxin in IgE-mediated rhinoconjunctivitis

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Key words: allergic inflammation; allergic rhinoconjunctivitis; eotaxin.

RECRUITMENT of eosinophils to the site of inflammation is mediated by numerous cytokines (CC). Among these CC, the chemokine eotaxin has been shown to possess unusual selective chemotactic activity (1,2). In a number of

studies it has been shown that an increase in the serum level of eotaxin is induced by allergen exposure (3,4). However others factors influencing the content of eotaxin in serum are still unclear. In this study we examine the role of age and sex on serum eotaxin in healthy volunteers (H) and subjects with intermittent allergic rhinoconjunctivitis (AR) (5).

The level of serum eotaxin was measured by ELISA (KITS, R&D, USA, pg/ml) in 64 healthy people (46 women; 18 men) and 122 with AR (44 women; 78 men) before the pollen season. Data were analyzed with the statistical package (STATISTICA (version 5.1) for WINDOWS). The student *t*-test was used for inter-group comparison.

A relation with age and sex only in allergies.

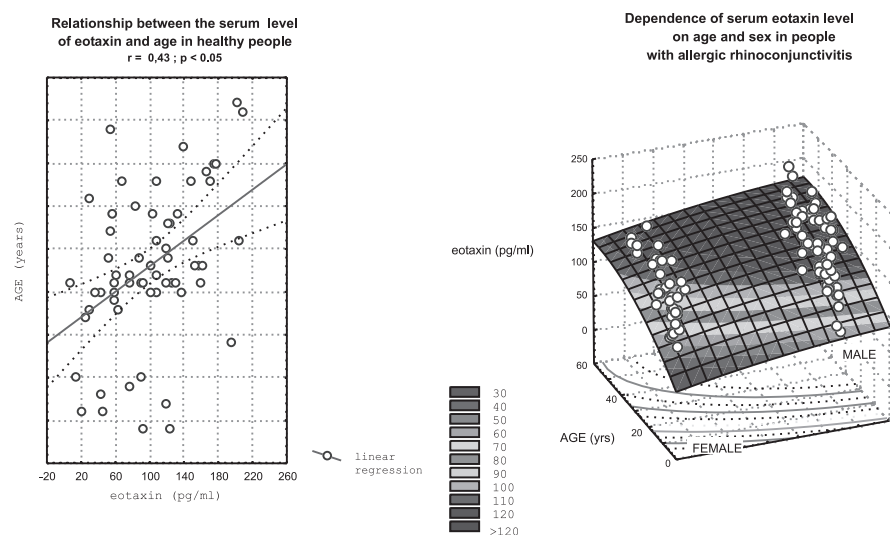


Figure 1. Regression models of influence of age and sex on the serum level of eotaxin in healthy (Formula A) and allergic people (Formula B).

There was no significant difference in the mean age of the allergic and healthy groups (AR: 30.0 years (SD 10.6); H: 28.2 years (SD 8.9); $P = 0.2$). The mean serum eotaxin concentration was higher in AR, but the difference between the groups was not statistically significant (AR: 114.1 (SD 45.5); H: 100.6 (SD 50.5); $P = 0.07$). A relationship between serum eotaxin level and sex and age in AR was noted; in this group the lowest concentration of eotaxin was observed in women younger than 25 years (81.8; SD 35.3) and the highest concentration was observed in men older than 35 years (145.5; SD 52.6).

A multiple regression model was derived for the influence of age and sex on the serum level of eotaxin in the allergic and healthy groups using two formulae:

Formula A: eotaxin (0.7)

$$= 2.6 \times \text{age (19.6)} + 31.8 \pm 47.1 \\ (R = 0.43, P < 0.00038)$$

Formula B: eotaxin (0.3)

$$= 1.4 \times \text{age (7.2)} + 31.7 \\ \times \text{sex (16.2)} + 21.26 \pm 38.2 \\ (R = 0.47, P < 0.000001)$$

A statistically significant multiple linear correlation was found (Fig. 1) (formula B) between age (semipartial correlation $\alpha = 0.33$, $P = 0.00003$) and sex (semipartial correlation $\alpha = 0.35$, $P = 0.00008$) on the one side, and the

serum level of eotaxin in on the other in the AR group. In the H group there was a linear correlation between age (semipartial correlation coefficient $\alpha = 0.414$, $P = 0.0006$), while no significant linear correlation was found for sex (semipartial correlation factor $\alpha = 0.18$, $P = 0.16$). The regression model describing the influence of age on the serum concentration of eotaxin in healthy subjects is presented as Formula A.

To our knowledge, no study concerning a correlation between the serum level of eotaxin and age in allergic or healthy people has been published so far. Neither have we found any publications about a relationship between the serum concentration of eotaxin and sex. However, it is known that male sex is related to allergic sensitization and higher production of Ag-specific IgE (6,7). In our opinion, this study suggests that age and sex are important determinants of the serum content of eotaxin in patients with intermittent IgE-mediated rhinoconjunctivitis. Further studies should elucidate why sex has different effects in people with allergies and those without.

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The biology of cypress allergy

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Key words: allergy; asthma; Cupressaceae; epidemiology; pollinosis.

Winter rhinoconjunctivitis caused by cypress allergy represents an emerging cause of morbidity in young adults living in the Mediterranean area, where ornamental use of both *Cupressus arizonica* and *C. sempervirens* has spread in recent years (1,2).

Approx. half of IgE-sensitized are symptom free.

Despite emphasis in describing this pollinosis as an emerging one, population-based studies on cypress allergy and sensitization are lacking. Our epidemiological survey was designed to assess the prevalence of symptomatic oculorhinitis and asymptomatic cypress sensitization in a cohort of 3434 subjects living in central Italy (Perugia county, Umbria region). Data were collected using a modified questionnaire of the European Community Respiratory Health Survey (3). Subjects had skin prick tests (SPT) with *Dermatophagoides*, *Alternaria tenuis*, *Parietaria officinalis*, Graminaceae mix, *Olea europaea*, *Cupressus arizonica* and *C. sempervirens* extracts (ALK-Abellò and Lofarma, Milan, Italy), by a standard procedure. Specific IgE levels were determined with commercially available reagents.

To categorize enrolled subjects (4), we applied a clinical score for absence (0 points) or presence (3 points) of symptoms, and a laboratory score from 0 to 3 points for cutaneous wheal and flare reactions plus 0–3 points for IgE antibody levels (RAST class from I to IV) to cypress extracts.

Table 1 summarizes the distribution of cypress allergy and sensitization in our study population. Among group A subjects, 103 (84.4%) were mono-sensitive to cypress pollen, whereas the remaining 19 (15.6%) were also sensitive to perennial and/or seasonal allergens. The frequency of self-reported asthmatic symptoms was less than 1% (one subject). Group A patients had fewer atopic members in

their first-degree relatives, compared to other groups.

SPT and/or RAST give information merely on sensitivity to individual allergens (5); 4.9% of our subjects were clinically asymptomatic but, nonetheless, had positive SPT and/or measurable IgE antibody levels. Therefore, assuming sensitization to cypress pollen as study end-point, would lead to a disease prevalence over-estimation (up to 8% of the total study population), similar to that previously published (1,2).

The virtual absence of asthma has been noted for other Cupressaceae species, such as the respiratory allergy to *Juniperus sabinoideis*, and recently confirmed in a survey on asthmatic children living in the south-east of France (6,7).

In conclusion, in areas (such as central Italy) in which cypress trees have been a common feature for centuries, cypress hypersensitivity is relatively low. Nonetheless, the widespread use of such trees justifies the major attention we now pose in diagnosing this particular winter allergy.

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Food allergy to pork meat

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Key words: childhood asthma; dust mites; pork allergy.

Although pork allergy is rare in childhood it may manifest in a variety of ways: urticaria, oral allergy syndrome (OAS) and exacerbation of an atopic eczema/dermatitis syndrome (1).

We report on a four-year-old boy with atopic eczema/dermatitis syndrome, AEDS and asthma due to sensitization to the house-dust mite *Dermatophagoides pteronyssinus*, and who had an anaphylactic reaction a few minutes after eating pork meat.

Unusual case with IgE antibodies to cooked and roasted meat

Table 1. Distribution of cypress allergy or sensitization in a population of 3434 young adults of central Italy

	Number	Prevalence (%)	Features of cypress sensitivity	Familial atopy
Group A	122	3.6	Oculo-rhinitis, positive SPT and detectable IgE antibody	19.5%*
Group B	167	4.9	Positive SPT and detectable IgE antibody	40.3%
Group C	539	15.7	None	38.9%
Group D	2606	75.8	None	No

Allergic subjects (group A) reached a total score = 7, by adding the 3 clinical symptom points to the sum of the laboratory score. Group B consisted of atopic subjects (0 point clinical score), identified as cypress-sensitized on the basis of the laboratory score only. Control groups were atopic subjects (group C) suffering from seasonal or perennial rhinitis due to other inhalant allergens; group D nonatopic healthy subjects. Statistical evaluation was performed by two dimensional contingency tables and Pearson's chi-squared tests with SPSS software.

* $P < 0.001$ vs. groups B and C.

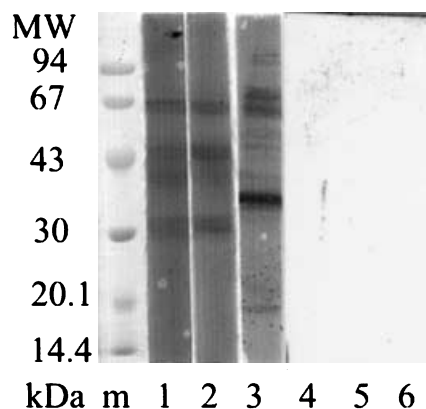


Figure 1. Immunodetection of pork meat and dust mite allergens: lane 1, cooked pork; lane 2, roasted pork; lane 3, dust mite extract; lane 4, cooked pork (control); lane 5, roasted pork (control); lane 6, dust mite extract (control).

Examination of the patient included cutaneous (skin prick test – SPTs, prick prick test – PPT), serological and provocative diagnostic tests with commercially available allergenic extracts (Torlak, Yugoslavia). Open challenge with food was carried out according to instructions given in an EAACI position paper (2).

Pork meat (cooked and roasted) was homogenized and extracted as a 20% suspension for 3 h in 0.2 M PBS, pH 7.2. Allergenic molecules were detected by Western immunoblot according to Harlow & Lane (3).

SPTs were positive for pork meat (+ +) and dust mite allergens (+). PPT with fresh food was positive only to pork meat. Open challenge with the pork meat induced, after a few minutes, generalized urticaria with intensive itching in the throat and eyes, and swelling of the lip, tongue, palate and throat.

The patient's serum reacted moderately to Dp (13.1 kU/l, class 3), whereas specific IgE to pork meat was undetectable. The total IgE was five times higher (223 kU/l) than the value usual for his age.

In Western blot (Fig. 1), six pork meat allergens (67 kDa, 65 kDa, 45 kDa, 43 kDa, 40 kDa, 31 kDa and 30 kDa) were detected in both extracts, and 11 dust mite allergens in range from 97 kDa to 20 kDa.

This is a first case of IgE-mediated food allergy to pork meat in a child with sensitization to dust mite allergens. Our results revealed that cooked and roasted pork meat retained allergenic epitopes

capable of inducing IgE-mediated food allergy.

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VCAM-1 in conjunctival inflammation

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Key words: conjunctival epithelial cells; dry eye; VCAM-1 expression.

DRY EYE IS a major cause of ocular discomfort, affecting millions of people throughout the world.

Dry eye has been defined as “a disorder of the tear film due to tear deficiency or excessive evaporation that causes damage to the interpalpebral ocular surface and is associated with symptoms of discomfort” (1).

Presence of activated T cells and pro-inflammatory cytokines has been found both in patients with Sjogren syndrome and with non-autoimmune dry eye (2). Therefore, both in Sjogren's syndrome and non-autoimmune dry eye, there is an immune-based inflammation that can occur locally in absence of systemic

An overexpression is found in "dry eyes".

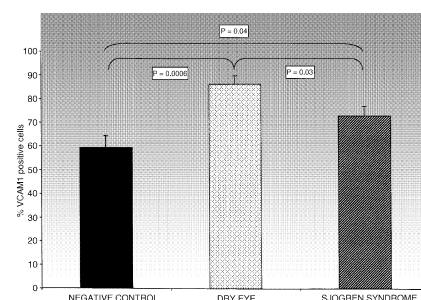


Figure 1. Percentages of VCAM-1 expression on positive conjunctival epithelial cells in patients with dry eye, Sjogren syndrome, and negative controls.

autoimmunity and is able to cause an abnormal ocular surface epithelium (3).

In this context, adhesion molecule expression on epithelial cells plays a crucial role in the conjunctival infiltrative mechanism, as extensively reported in the model of allergic conjunctivitis (4).

VCAM-1 is a cell surface glycoprotein of the Ig gene superfamily, and its increase in episodes of acute inflammation is associated with a T cell and monocytic infiltrate (5). Because VCAM-1 binds to the integrin VLA4 on the surfaces of lymphocytes and monocytes, VCAM-1 may be responsible for recruiting immune cells to sites of active inflammation (6).

The aim of the present study was to investigate the expression of VCAM-1 on epithelial conjunctival cells of patients with Sjogren syndrome. Twenty-two patients with Sjogren syndrome (53.2 ± 11.1 years old, 1 male and 21 females), 12 patients with dry eye (54 ± 12.7 years old, 2 males and 10 females), and 10 normal subjects (39.4 ± 12.6 years old, 3 males and 7 females) were studied.

All patients were symptomatic for more than 4 months when they were studied.

The study was performed according with the declaration of Helsinki and it was approved by our Ethics Committee.

All subjects gave their informed consent for ophthalmologic procedures. No subject received a steroid or anti-inflammatory drug for at least 1 month.

Cytological specimens were collected by the impression process. VCAM-1 expression was evaluated by the immunostaining procedure.

VCAM-1 expression was detected in all samples. VCAM-1 expression was higher

in patients with Sjogren syndrome and dry eye than in normal subjects. Moreover, patients with dry eye showed a significant difference in comparison with normal subjects ($P = 0.0006$) and with patients suffering from Sjogren syndrome ($P = 0.03$). Patients with Sjogren syndrome showed a significant difference in comparison with normal subjects ($P = 0.04$).

VCAM-1 is an adhesion molecules involved in cellular recruitment: in fact, its expression may be regarded as a marker of a broad range of inflammatory diseases.

The meaning of our findings is consistent with the pathophysiological mechanisms involved in the immuno-mediated inflammation occurring in dry eye disorders.

The overexpression of VCAM-1 in all dry eye disorders is dependent on the presence of lymphocyte activation, which has been previously demonstrated in all dry eye disorders (1,2).

In conclusion, this study is the first evidence concerning the overexpression of VCAM-1 involved in the inflammatory response associated with dry eye.

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Severe cow's milk allergy

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Key words: allergy; infants; life-threatening; milk protein.

COW'S MILK protein allergy (CMPA) is a form of food-induced allergic reaction that usually appears during infancy (1,2). CMPA may involve the gastrointestinal tract, the respiratory tract, or the skin (1). Symptoms may manifest as an acute episode—at times life-threatening—or may have a more chronic form (1, 3). Immediate hyper-sensitivity reactions to cow's milk (CM) are usually IgE-mediated. However, the food protein-induced enterocolitis syndrome (FPIES) is not IgE-mediated (3).

We present a series of four babies that presented with severe life-threatening episodes, all related to unsupervised self-challenge with either a CM-based formula or a dairy product. Parental decisions, physician recommendations, or inadvertent ingestion resulted in these serious clinical presentations.

Case 1: A 5-month-old boy presented with vomiting, bloody diarrhea, severe lethargy, and shock, that developed within hours of exposure to a dairy product. Previous exposure to a CM-based formula had resulted in respiratory distress, wheezing, and hematochezia. A presumptive diagnosis of CMPA was made and a semi-elemental formula for feeding was recommended. He subsequently had two similar episodes on re-exposure to CM. Parental consent to a skin test could not be obtained.

Case 2: A 6-week-old girl presented with emesis and diarrhea a few hours

after ingesting a CM-based formula. A presumed diagnosis of CMPA was made and a semi-elemental formula diet was started. A trial of CM-based formula feeding on a pediatrician's recommendation at the age of 4 months led to a state of lethargy, peripheral cyanosis, vomiting, and profuse diarrhea, within 15 min of ingestion. A skin prick test was negative for CM and soy proteins.

Case 3: A 6-month-old boy presented with multiple episodes of vomiting, profuse watery diarrhea, and severe lethargy. This began 2 h after exposure to a commercial baby pudding containing CM. Past history included several episodes of fever, vomiting, and diarrhea after exposure to a CM-based formula. A skin test was negative for CM or soy proteins.

Case 4: A 5-month-old boy presented with fever, lethargy, and recurrent vomiting which started 2 h after ingesting a dairy product. Before this episode he had been fed solely on breast milk, except for a single trial of CM-based formula at age 3 months, which was followed by fever, vomiting, and a skin rash. A skin test was positive for CM and soy protein antigens.

In all four cases other possible etiologies with similar presentations were excluded.

Avoidance of CM-based formula was recommended in all cases. None of the children had a personal or family history of allergic diseases.

In a recent position paper (4), Johansson et al. suggested an updated nomenclature for food allergies. They suggested that an adverse reaction to food should be called food hypersensitivity. When immunologic mechanisms are demonstrated, the appropriate term is food allergy; and if the role of IgE is highlighted, the term is IgE-mediated food allergy.

The common element for all these cases was that all the children had demonstrated a previous serious reaction to CM protein. Despite warnings given to the parents of the dangers of CM ingestion, all the children been re-challenged with CM protein either because of a parent's decision or a physician's advice.

One infant (case 4) was confirmed to have IgE-mediated immediate hypersensitivity to CM and soy proteins by a positive skin test. Another infant's clinical picture (case 1), although not proven by skin test, was compatible with this type of hypersensitivity. The two other cases

Near-fatal reactions in four children.

(2 and 3), whose skin tests were negative, were compatible with the diagnosis of FPIES. This is a non-IgE-mediated form of acute allergy to CM or other allergens. It is a disorder of early infancy, manifesting within hours of exposure with vomiting and diarrhea, and it may result in dehydration. Hypotension is not uncommon, fecal occult blood is often positive, and an elevated polymorphonuclear blood count is typical. Skin prick tests are negative in most cases (3). Diagnosis of this disorder is based on clinical and challenge criteria (3).

In conclusion, food allergy and FPIES in particular must be considered in the differential diagnosis of repeated shock-like episodes, or severe gastrointestinal symptomatology related to feeding in infants.

The appropriate guidance to families regarding strict elimination of CM or soy protein from the diet is crucial.

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Simultaneous drug allergies

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Key words: clavulanic acid; moxifloxacin; betalactams; penicillin; quinolones; drug allergy.

WE REPORT THE CASE of a 32-year-old woman who developed a generalized urticaria 15 min after the intake of amoxycillin-clavulanic acid (AX/CL) (500/125 mg) (Augmentine™, GlaxoSmith Kline, Madrid, Spain). The reaction subsided with methylprednisolone and dexchlorfeniramine administered at the emergency room. After this reaction the patient tolerated a 7-day course of AX. One year later, she presented a nonitching micropapular exanthema some hours after the intake of 400 mg moxifloxacin (MX) (Octepra™, Grupo Vita, Spain), which resolved in 3 days with dexchlorfeniramine. One year after the latter reaction the following allergological study was performed. Written informed consent was given by the patient.

Skin prick tests (SPTs) and intradermal tests (IDTs) with benzylpenicilloyl poly L-lysine (PPL) and minor determinant mixture (MDM) (Allergopen™, Allergopharma, Reinbek, Germany), benzylpenicillin (BP) (10,000 UI/ml), AX (25 mg/ml) and AX/CL (25/5 mg/ml) yielded negative results. Specific IgE (Pharmacia CAP System, Uppsala, Sweden) to benzylpenicilloyl, fenoxymethylpenicilloyl, AX and ampicillin were also negative. An oral challenge with increasing doses of AX/CL up to 500/125 mg was well tolerated.

Fifteen days after this first negative study the patient was re-evaluated. An immediate positive IDT with AX/CL was found (10 mm wheal, 27 mm erythema). CL (Beecham, Spain) was tested separately in a saline solution at 1 and 10 mg/ml. These two concentrations do not induce nonspecific skin tests reactions in controls (1,3). SPTs with CL were negative, but an immediate IDT reaction was observed with 10 mg/ml (12 mm wheal, 28 mm erythema). The remaining skin

tests and specific IgE determinations were negative. A histamine release test (HRT) with BP, AX and CL was performed following an automated fluorometric method previously described (1). No release was observed with BP and AX, whereas CL induced a dose-related response with a maximum release of 50% with 200 µg. The CL concentrations used did not induce histamine release in controls (1). One year later IDT and HRT with CL yielded again positive results.

SPTs performed with MX at 1 and 10 mg/ml, and a patch test (10% in petrolatum) were negative. Higher concentrations of MX induced nonspecific SPT reactions in control subjects. HRT with MX and ciprofloxacin yielded high peaks in the patient and control tests, probably because of an interference with the fluorometric method of histamine determination, as already described with quinolones (2). Twenty hours after the oral administration of MX (up to 400 mg) the patient developed a mild pruritic micropapular exanthema which resolved with oral prednisone and cetirizine in 48 h. No reaction was observed with the related quinolones piperimidic acid, norfloxacin and ciprofloxacin, neither in SPTs (1 mg/ml), IDTs (0.001–1 mg/ml) and patch tests (10% in petrolatum), nor after their oral administration.

The results of the allergological study performed (positive IDT and HRT to CL) suggest that the immediate reaction induced by AX/CL in our patient was due to a specific immunologic mechanism towards CL. Clavulanic acid is a betalactam antibiotic with weak antibacterial activity, but a potent inhibitor of betalactamases. Despite its wide use in association with AX, there are only three reported cases of allergic reactions to CL (1,3), in all of which an immediate immunologic mechanism was also involved. As with our patient, two of the previously reported cases (1) had no reactivity to other betalactams. This specificity in the immunologic response to CL might be related to differences in its structure and metabolism, which can generate metabolites not related to those derived from BP (4).

Moxifloxacin is a fluorquinolone antimicrobial agent recently marketed, and only two anaphylactic reactions have been reported so far (5). MX induced in our patient a delayed reaction

(exanthema) in which an immunologic mechanism, probably directed to a specific MX metabolite, seems to be involved. This could explain the negativity of the tests performed with the native drug, as well as the lack of cross-reactivity with other quinolones, in contrast to previous reports (2).

In summary, this patient combines two exceptional selective immunologic reactions to two unrelated drugs: an immediate reaction to the betalactam CL, and a delayed reaction to the quinolone MX.

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Adverse reactions to pyrazinamide

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Key words: Tuberculosis; pyrazinamide; hypersensitivity; rash; desensitization.

CUTANEOUS REACTIONS to antituberculosis drugs are common. We de-

scribe a case of immediate cutaneous reaction to pyrazinamide without previous exposure.

A 41-year-old Latino-American woman without prior antituberculous treatment was diagnosed having active lung tuberculosis. Rifampicin (600 mg/day), isoniazid (INH) (300 mg/day), pyrazinamide (1500 mg/day), ethambutol (800 mg/day), and pyridoxine (40 mg/day) were prescribed. Treatment was started with a single dose of INH and rifampicin. The three other drugs were added the following morning. Within minutes, she developed a flush with nausea, dyspnea and abdominal discomfort followed by an itchy rash. All drugs were stopped and clemastine was administered. The skin eruption disappeared within 24 h and did not recur after sequential challenge with rifampicin and isoniazid first at reduced, then at full dosage. After administration of 500 mg of pyrazinamide, she developed an identical skin rash within half an hour. Challenge with ethambutol was well tolerated. Pyrazinamide was replaced by ciprofloxacin in our case.

Pyrazinamide has gained importance in the past years as the incidence of multiresistant tuberculosis is rising. It was synthesized in the 1950's following the observation that nicotinamide was effective in the treatment of experimental tuberculous infections. The mechanism of antituberculous action is not completely understood. Liver injury is the most serious side-effect. Other side-effects include hyperuricemia, anorexia, nausea, vomiting, arthralgia and fever. Photosensitivity, skin rashes, flushing and pelagra have been reported.

Hypersensitivity reactions to antituberculous drugs usually appear within 3–7 weeks after initiation of treatment. The incidence of cutaneous reactions due to pyrazinamide is not quantified. It seems, however, that the skin reactions to other antituberculous drugs are far more frequent (1): 2% of more than 2000 patients treated with isoniazid presented a skin rash as the most common adverse effect. Another series with almost 2000

Immediate skin rash at initiation of anti-tuberculosis therapy.

patients treated with ethambutol revealed an incidence of 0.5%. Rifampicin caused skin rash in 0.8% of patients. Cutaneous hypersensitivity reactions to antituberculous drugs are more frequent and more severe in HIV-positive patients (2).

Nicotinamide from which pyrazinamide has been synthesized regularly causes truncal and facial flushing and itching. These reactions appear to be prostaglandin-mediated and can be prevented by aspirin (3). One could hypothesize that a similar mechanism is responsible for pyrazinamide-induced flushing and skin rash.

Pyrazinamide accounted for four other cases of immediate skin rash after first dose of antituberculous regimen (4–6). Flushing has been described in one patient (4). In two cases re-administration of pyrazinamide caused a similar rash. Pyrazinamide can be tolerated after reintroduction at a lower dose followed by a stepwise dose increment (6).

In conclusion, pyrazinamide should be suspected if an immediate skin rash develops at initiation of antituberculosis chemotherapy. If the skin involvement is not severe, sequential reintroduction of the drugs first at low, then at full dosage should be attempted. Pyrazinamide should be reintroduced last and at low dose.

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IgE antibodies to penicillin in skin test negative patients

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Key words: IgE antibodies; immediate reactions; *in vitro* test; penicillin allergy; skin test.

SKIN TESTS (ST) are reported to be more sensitive than *in vitro* tests for determining IgE antibodies to beta-lactams.

However, evidence exists of *in vitro* positivity with ST negativity in patients allergic to penicillins, but the number of cases was limited and the report is more than 20 years old (1), so that a re-evaluation seems necessary.

We studied a group of subjects with an immediate allergic reaction to a penicillin derivative who were ST negative with a validated standard of classical and side chain penicillin determinants, but who had in their serum IgE antibodies to a penicillin derivative. STs were performed using PPL 5×10^{-5} mmol/l, MDM 2×10^{-2} mmol/l (Allergopharma, Merck, Darmstadt, Germany), AX 20 mg/ml (Beecham, Toledo, Spain) and AMP 20 mg/ml (Antibiotic SA, León, Spain) (2). IgE antibodies were measured using RAST to benzylpenicilloyl-poly L-lysine (BPO-PLL) and amoxicylloyl-poly L-lysine (AXO-PLL) (3). A drug provocation test (DPT) was made administering increasing doses of benzylpenicillin (BP) and amoxicillin (AX) at 1-hour intervals (2). Two control groups were evaluated: negative, 40 nonallergic subjects with negative STs to all haptens and good

tolerance to BP and AX; and positive, 40 patients with ST positive to at least one of the haptens and RAST positive to BPO-PLL or AXO-PLL.

Of 290 patients with immediate allergic reactions to a penicillin derivative, 40 (13.8%) were ST negative and RAST positive. The diagnosis was confirmed because five developed systemic symptoms after ST, 11 developed more than one reaction with penicillin derivatives according to the clinical history, and in 24 it was confirmed by DPT. Twenty-three were female and 17 male, the mean age was 44.5 ± 14.6 years, 28 had developed anaphylaxis and 12 urticaria. AX was the drug involved in 26 cases, un-recalled penicillin in 6, ampicillin in 5, BP in 2 and cloxacillin in 1. The mean interval between the occurrence of the reaction and the study was 252 ± 281 days. In 13 cases (32.5%) the RAST was positive to both haptens, in nine (22.5%) only to BPO-PLL and in 18 (45%) only to AXO-PLL. Comparison with the positive control group showed no significant differences in age, sex, time interval, or RAST values. Linear regression analysis showed no significant association between the RAST value and the time interval, either in the patients or in the positive control group. None of the subjects in the negative control group had a positive RAST.

It is generally considered that a subject with a positive history of penicillin allergy but who is ST negative is likely to tolerate the drug (4), but patients allergic to penicillins may be ST negative and develop an allergic response after exposure (2). Confirmation of the diagnosis in these subjects is difficult since the DPT may involve significant risks. These subjects not detected by skin testing led us to consider alternative methods to confirm the diagnosis whilst avoiding DPT. A specific IgE antibody assay is a good alternative approach in persons with a history of penicillin allergy but who are ST negative. Whether this can be extended to other beta-lactams, such as cephalosporins, is at present being studied.

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AAE and IgA myeloma

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Key words: acquired angioedema; C1-inhibitor deficiency; carcinoid tumor; monoclonal gammopathy.

A 72-YEAR-OLD WOMAN was admitted for evaluation of

recurrent, non-pruritic, edematous attacks occurring

on the face, lips and uvula, and which did not affect the airways. The patient had no personal allergic history or family history of angioedema. Attacks resolved

Acquired Angioedema type II in a case of carcinoid tumor

Abbreviations: AAE: acquired angioedema; C1-INH: C1 esterase-inhibitor.

Table 1. Characteristics of C1 inhibitor, complement, IgA and IgG

	Patient's values	Normal range
C3 (mg/dl)	121	90–180
C4 (mg/dl).	< 1.38	10–45
CH50 (U/ml)	< 25	150–250
C1INH (mg/dl)	12	15–40
IgA (mg/dl)	1050	70–400
IgG (mg/dl)	723	700–1600
Functional activity of C1 inhibitor		80–100%
Control plasma	100%	
Patient's plasma	0%	
Patient's plasma with control plasma	7%	
Patient's IgA with control plasma	0%	
Patient's IgG with control plasma	80%	

spontaneously or after treatment with low doses of oral corticosteroids for 2–3 days. A complement profile revealed: CH50 less than 25 U/ml, C4 less than 1.38 mg/dl, C1 inhibitor 12 mg/dl (15–40) and normal C3 at 121 mg/dl. Serum IgA 1050 mg/dl (n: 70–400), IgG and IgM were normal. Electrophoresis showed a distinct abnormal band in the beta region. Serum immunoelectrophoresis revealed an IgA lambda paraprotein. Spirometric values showed a moderate restriction with forced vital capacity of 71%. A chest radiograph revealed a loss in volume of the left hemithorax with a left upwards hilar traction and poor delimitation of the lower left cardiac edge, compatible with an atelectasis of the left upper lobe. Computerized axial tomography of the chest confirmed the presence of the atelectasis. Computerized axial tomography of the abdomen was normal. Analysis of bone marrow revealed a monoclonal IgA-lambda population of plasma cells, without evidence of overt myeloma. One hour before bronchofiberscopy, replacement therapy with 1000 units of C1-INH concentrate (Berinert P. Aventis Behring GmbH Marburg, Germany) was administered to the patient. Bronchofiberscope revealed a smooth and fungate rounded mass protruding into the left main bronchus, suggestive of a carcinoid tumor. A pulmonary biopsy was also carried out and it was compatible with carcinoid tumor. Because of the potentially lethal nature of these attacks, 2 mg stanazolol twice daily was started. In January 2001, the patient underwent surgery for her carcinoid

tumor. Six months after the operation, the patient had not had attacks of angioedema, while complement component levels and IgA levels continued to be abnormal. She is still under treatment with 2 mg stanazolol once daily.

To demonstrate that there was an agent in the patient's plasma that inhibited the C1 inhibitor, we incubated the patient's plasma with plasma from a healthy blood donor (1/1) for 18 h at 4°C. Another serum diluted 1/1 in PBS and incubated in the same conditions was used as a control. To assess whether monoclonal antibody was responsible for C1 inhibitor inactivation, we incubated separately the isolated IgA paraprotein and polyclonal IgG obtained from the patient, with a plasma specimen from a healthy blood donor (1/1) for 18 h at 4°C. Monoclonal IgA completely abrogated C1 inhibitor activity of the control plasma. The results are expressed in Table 1.

AAE type II is characterized by the presence of autoantibodies to C1 inhibitor (1,2). Indirect evidence suggests that these antibodies could be paraproteins in some cases, but so far this assessment has not been completely demonstrated (3). We have studied a patient with acquired autoimmune C1-INH deficiency. We could demonstrate that IgA paraprotein was responsible for C1 inhibitor inactivation. To the best of our knowledge, this is the first case of AAE that directly demonstrates the anti C1-INH activity of a monoclonal paraprotein. A review of the literature suggests that this is the first case of acquired angioedema associated with a carcinoid tumor.

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Carcinoid behind baker's asthma

J. Walusiak*, C. Palczynski

Key words: bakers' asthma; carcinoid; hypersensitivity to flour.

BAKERS' ASTHMA is one of the most common occupational allergic diseases.

It is estimated that 5–10% of bakers suffer from asthma and 14–39% from allergic rhinitis (1).

However, it has been estimated that about 30% of bakers sensitized to occupational allergens do not display work-related symptoms (2). The prevalence of IgE antibodies has been reported to be high, e.g., in Baur et al. study 53% of examined bakers had IgE antiwheat flour (1). It should be also noted that about 30% of bakers reporting work-related chest symptoms do not demonstrate IgE antibodies to occupational allergens (1).

Bronchial provocation and bronchoscopy might be considered in unusual cases.

We present the case of a 25-year-old baker, who had worked in a bakery for 10 years, and was admitted to the Department of Occupational Diseases with the suspected diagnosis of occupational asthma. The patient had been suffering from attacks of cough and dyspnoea for 3 years. Symptoms were aggravated by contact with flour and the patient reported only slight improvement when away from work. Signs of allergic rhinitis had not been reported. 2.5 years before admitting to our Department, bronchial asthma had been recognized in the patient and standard anti-asthmatic treatment was applied. However, the symptoms were poorly controlled by high doses of inhalant glucocorticosteroids and due to their severity he was hospitalized three times at pneumonology departments. On admittance, a clinical examination revealed increased blood pressure (180/120 mmHg). The routine laboratory parameters, as well as the chest X-ray remained normal. Total IgE (CAP System, Pharmacia, Uppsala, Sweden) level was elevated (132,0 kU/l). IgE antibodies specific to wheat, barley and rye flour allergens (Phadezym fx20, Pharmacia, Uppsala, Sweden) were found (class 1). Furthermore, skin prick tests to *Dermatophagoides farinae* and *Acarus siro* (Allergopharma, Reinbek, Germany) were positive. FEV₁ was 87% of predictive value and the histamine provocation test did not reveal bronchial hyperreactivity. Specific inhalation challenge with flour and bakers' additives did not induce any decrease in FEV₁ and PEF_R or increase in bronchial hyperreactivity. Because of the negative result of provocation test and the presence of hypersensitivity to occupational allergens, the patient was subsequently subjected to bronchofiberscopy to evaluate bronchoalveolar lavage (BAL) before and after specific challenge. However, the BAL could not be taken, since at the beginning of bronchofiberscopy we discovered tumor in the left bronchi. The histopathological analysis of taken biopsy specimen identified it as carcinoid. The urine excretion of the serotonin metabolite 5-hydroxyindoleacetic was above normal range (315 µmol/day). The patient successfully recovered after left-side lobectomy and has been free from all previous symptoms, i.e., cough, dyspnoea and hypertension for a 1.5-year.

For a long time, our patient had been mistakenly diagnosed with bronchial asthma rather than carcinoid syndrome. In fact the patient did not display bronchial hyperreactivity, but in a patient reporting dyspnoea, with the obturation changes in spirometry, histamine test is not routinely performed. On the other hand, carcinoid occurs rarely and usually the most common and the earliest sign is the flushing, which was not reported by our patient. The hypertension was not revealed before hospitalization at our Department. In a patient occupationally exposed to strong asthmogens, sensitized to flour and reporting attacks of dyspnoea, wheezing during the auscultation, the recognition of asthma seemed the most probable. Although occupational asthma is sometimes based on the hypersensitivity to occupational allergens, found by skin prick tests or estimation of IgE antibodies, the presented case confirms again the general opinion that the specific inhalation challenge should be the gold standard in the diagnostics of occupational asthma.

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Urticaria caused by cola drink

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Key words: caffeine; cola drink; oral challenge; urticaria.

We report on a patient who developed urticaria after the ingestion of cola

A case of generalized non-allergic urticaria to caffeine.

drinks. A 16-year-old woman, with personal and family history of atopy (hay fever), had suffered from recurrent acute episodes of generalized urticaria after ingestion of cola drinks (Coca-Cola®) in the last 8 years. She noticed that the larger amount she drank, the more severe the skin rash. In one occasion, she needed emergency treatment because of her symptoms. She did not drink coffee or tea, and tolerated chocolate without any ill effect. She had no history of any adverse drug reactions. Skin prick tests with a regular cola drink (Coca-Cola® as is) and cereal flour (wheat, rye, barley and oat) extracts 10% w/v were all negative. A double blind, placebo-controlled, oral challenge test, was performed with a regular cola drink (Coca-Cola®) and a decaffeinated cola-drink. Oral challenge with the regular cola-drink provoked itching and urticaria on her trunk and legs within 10 min after administration of 630 ml. However, oral challenge with the caffeine-free cola-drink elicited no adverse reactions. Thus, we suspected that caffeine might be the agent responsible for her allergic symptoms. A skin prick test with caffeine (10 mg/ml) was negative. However, a positive intradermal test (10 mm wheal with erythema) was obtained with caffeine at 1 mg/ml. The same test performed in five atopic patients elicited no response.

A double blind, placebo-controlled oral challenge with caffeine (50 mg) administered in green opaque, tartrazine-free capsules produced itching and urticaria on the face, neck and trunk. The patient required treatment with oral antihistamines, corticosteroids and subcutaneous epinephrine to control her symptoms.

Caffeine is an amine presents in beverages such as coffee, tea, cola drinks and chocolate. It is a methylxanthine closely related to theophylline and theobromine. Allergy-like hypersensitivity reactions caused by caffeine are uncommon. However, the oral challenge tests performed in this patient confirm that caffeine was the substance responsible for the development of urticaria after drinking cola drinks.

We have no evidence to implicate an immune mechanism as being responsible for this reaction to caffeine, and a pharmacological mechanism is also very unlikely since xanthines themselves are inhibitors of the release of chemical mediators (1). Therefore, a personal susceptibility or non-allergic hypersensitivity pathway may be the underlying mechanism. In the previous case reports of urticaria caused by caffeine (2–4), the prick test with caffeine was positive in two out of three cases (2,4). However, the passive cutaneous transfer test (Prausnitz–Küstner) performed on one patient was negative (2). Urticarial reactions caused by aminophylline (5,6) have been reported, and have been considered secondary to the ethylene diamine portion of the aminophylline molecule (6).

Caffeine should be considered as a potential causative agent of urticaria induced by the ingestion of caffeine-containing beverages and drugs.

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The major allergen of linseed

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Key words: allergy; blot; dimer; flax; IgE; linseed; *Linum*.

LINUM USITATISSIMUM (FLAX) is a plant belonging to the Linaceae family. Its seeds have been used from the beginning of civilization for human and cattle consumption, and its fibres have always been of important commercial value in the textile industry. In our time, linseed oil is increasingly used as a laxative (1). Anaphylaxis induced by flax has been described (2,3), and a multimeric protein has been suggested as the allergen (2). We studied the IgE antibody specificity of a 39-year-old woman who suffered an anaphylactic reaction immediately after the ingestion of the first spoonful of grains of linseed, prescribed as a laxative.

A skin prick test with linseed was positive and IgE antibodies to linseed in serum (20 KU/l), with total serum IgE of 221 KU/l, was demonstrated by ImmunoCAP assay (Pharmacia Diagnostics) and by a positive Leukocyte Histamine Release Test. SDS-PAGE of linseed extract, stained with Coomassie (Fig. 1, panel A) showed clear differences between the β -mercaptoethanol-reduced (lane 1, main antigen approx. 55 kDa) and the non-reduced extracts (lane 2, main antigen c. 30 kDa). Western Blotting (Fig. 1, panel B), revealed specific reactivity towards one major allergen of approximately 56 kDa prior to reduction (lane 1). This reactivity was greatly abolished in the reduced sample, in which a 28-kDa band was the major allergen (lane 2).

This study strongly suggests that the implicated allergen is a dimer, consisting of monomers (28 kDa) bound by SH₂ groups. A candidate might be the malate dehydrogenase MDH-1 found in flax seeds, a dimer of identical subunits in the

A 28-kDa dimeric protein identified in *Linum usitatissimum*.

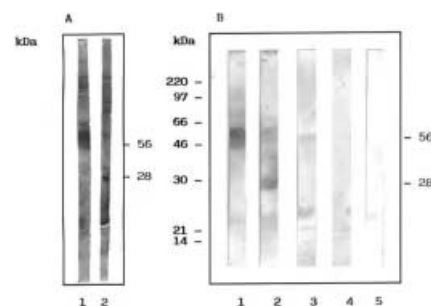


Figure 1. Panel A. Protein separation by 10% SDS-PAGE of linseed extract (40 µg/lane), in the absence (lane 1) or presence (lane 2) of β_2 -mercaptoethanol. Coomassie-blue staining of the gel. Panel B. IgE-immunoblotting of linseed extract (40 µg/lane) after protein transfer to PVDF membranes. Lanes 1 and 3, unreduced; lanes 2–5, reduced with β_2 -mercaptoethanol. Lanes 1 and 2, patient's serum; lanes 3 and 4, control serum. Lane 5, secondary antibody alone (goat anti-human IgE).

35 kDa range (4). From a clinical point of view, the increasing use of linseed as laxative in herbal medicine (usually without detailed labelling) and in multi-grain bread, implies a growing risk of hypersensitivity that should be taken into account.

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