Allergen Characterization of Chia Seeds (*Salvia hispanica*), a New Allergenic Food

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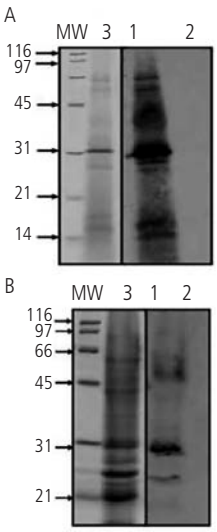
Palabras clave: Asma ocupacional. Metabisulfito sódico. Alergia pescados. Calamari.

Salvia hispanica, known also by its popular name, chia, is a plant of the Lamiaceae family. The plant is considered a pseudocereal and has a high oil and protein content. Mayans and Aztecs used it as a medicinal product and food supplement for added endurance. Its nutraceutical properties are due to high content in dietary fiber, natural antioxidants, and unsaturated fatty acids (60% α-linolenic acid). The protein content of chia is higher than that of most traditional grains. The plant contains storage proteins such as11S globulin (also known as α-conglutin, legumin, and glycinin), 7S globulin (also known as β-conglutin, vicilin, convicilin, and vicilin-type), 7S basic globulin (also known as γ-conglutin), and 2S sulphur-rich albumin (also known as δ-conglutin). The rest of the proteins are albumins, prolamins, glutelins, and insoluble proteins [1]. Although chia is not well known as a dietary supplement, its global production has increased in recent years due to its health properties and growing popularity.

To our knowledge, there are no cases in the medical literature describing allergic reactions due to chia seeds. There have, however, been a few cases of hypersensitivity reactions to plants from the same family (Lamiaceae), including anaphylaxis induced by menthol in toothpaste [2], contact dermatitis due to *Salvia officinalis* extract in cosmetic products [3], and a systemic allergic reaction following the ingestion of oregano and thyme [4]. In this article, we describe an anaphylactic reaction to chia seeds and characterize its allergens.

We report the case of a 54-year-old man with a previous diagnosis of rhinitis and asthma with sensitization to grass pollen and cat dander. A few days after starting to consume chia seeds—as a recommended means of lowering cholesterol levels—the patient noticed pruritus in his mouth and on the third day he developed generalized urticaria, and experienced facial angioedema, shortness of breath, and dizziness. He required emergency medical treatment to recover from these symptoms. He was evaluated in our outpatient clinic 2 weeks after the most recent episode. Skin prick tests were positive for allergy to pollen (grass, cypress, plane), profilin, and cat dander (ALK). Skin prick testing was negative for sesame, purified lipid transfer protein (Bial), and other commercial food extracts. The patient's tryptase levels were normal. Total IgE was 1592 kU/L. Prick-prick testing with chia seeds was positive (5x6 mm). Specific IgE results (in ISU units) (ISAC, Thermo Fisher Scientific) were as follows: rPhl p 1, 33; rPhl p 2, 50; rPhl p 4, 5.9; rPhl p 5, 0.6; nCyn d 1, 8; nCup a 1, 37; nCryj 1, 7.9; rFel d 1, 3.1; rVes v 5, 3.3; rPol d 5, 6; rBet v 2, 6.7; rHev b 8, 7.4; rMer a 1, 9.5; rPhl p 12, 2.7. The results for the rest of the allergens, including Ses a1, were negative. The ImmunoCAP results were <0.35 k/UL for *Thymus vulgaris* and *Menta piperita*, 0.43 k/UL for *Salvia officinalis*, and 0.61 for *Origanum majorana*. The patient reported no reactions to hymenoptera stings and stated that he had only experienced oral pruritus on eating sesame seeds, but not on all occasions.

Chia extract was prepared from the seeds of a commercial product. The seeds were dissolved in phosphate buffered saline and the proteins were extracted overnight at 4ºC with constant stirring. After centrifugation at 15000 g for 15 minutes, the supernatant (water soluble extract [WSE]) was collected. The pellet fraction was resuspended in water and stirred for 1 hour at 4ºC to remove any residual salt, and then centrifuged for 10 minutes at 15000 g. The pellet fraction was stirred for 1hour in 70% (vol/vol) aqueous ethanol at 4ºC and centrifuged. The supernatant was designated as the liposoluble extract (LE). The WSE was dialyzed against 100 mM NH_4HCO_3 and later lyophilized. The LE extract was concentrated and purified using the Amicon system (Milipore). The protein concentration was determined according to the method published by Bradford. SDS-PAGE, immunoblot, and identification of proteins by tandem mass spectrometry (MS/MS) were performed as previously described [5]. MS/MS analysis was performed in the proteomics department of the Universidad Complutense in Madrid (Spain), a member of the ProteoRed Network. SDS-PAGE of chia extracts revealed multiple protein bands with an apparent molecular weight ranging from 15 to 60 kDa and a common band around 31 kDa (Figure A,B). The liposoluble chia extract showed 3 IgE-binding bands with molecular sizes of around 15, 17, and 29 kDa (Figure A). The water-soluble chia extract showed 2 IgE-binding bands with molecular sizes around 25 and 46 kDa (Figure B). A common band around 31 kDa was detected in both extracts. The peptide sequences of the 29-kDa protein (LE) yielded a high match with lectins from related species such as *Phaseolus coccineus* and *Phaseolus vulgaris*, with a match identity of around 86% (Figure C). Peptide sequences of the 46-kDa IgE-binding band (WSE) exhibited a high degree of homology with elongation factor Tu from species such as *Medicago trucantula*, with a match



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IgE-Binding Band	Peptide Sequence	Identification	Amino Acid Similarity	Amino Acid Similarity and Conserved Substitution
29 kDa (LE)	AVEFDTLYNTNDPNYR	LECTIN	12/14 (86%) with *Phaseolus coccineus* and *Phaseolus vulgaris*	12/14 (85%)
46 kDa (WSE)	FDAEVYVLSKEEGGR	ELONGATION FACTOR TU	12/15 (80%) with *Medicago truncatula*	15/1S (100%)
31 kDa (WSE)	ESWDPNMR	11S GLOBULIN (Cupin-1)	6/8 (75%) with *Ricinus communis*, *Quercus robur*, *Ficus pumila* and *Juglans regia*	6/8 (75%)
19 and 17 kDa (LE)	GLDIDPYALLR VADIDPYAEPR	No No		
25 kDa (WSE)	No sequence found	No		

Figure. A, Liposoluble fraction from *Salvia hispanica*. Lane 1,SDS-PAGE immunoblots of liposoluble extract under reducing conditions. Lane 2, Patient serum. Lane 3, Control serum. B, Water-soluble fraction from *Salvia hispanica*. Lane 1,SDS-PAGE immunoblots of water-soluble extract under reducing conditions. Lane 2, Patient serum. Lane 3, Control serum. C, Identification of peptides from IgE-binding proteins by mass spectrometry. MW indicates molecular weight; LE, liposoluble extract; WSE, water-soluble extract.

identity of around 80% (Figure C). Peptide sequences of the 31-kDa IgE-binding band exhibited a high degree of homology with a legumin precursor (11S globulin) from species such as *Ricinus communis, Quercus robur, Ficus pumila*, and *Juglans regia*, with an identity match of around 75% (Figure C). No significant homologies were found for 25-, 17-, or 19-kDa IgE-binding proteins.

In summary, we have described the first case of an IgE-mediated anaphylactic reaction induced by chia seeds. The allergens involved are water-soluble and liposoluble and include a lectin, an elongation factor, and an 11S globulin as known allergens in addition to another 3 as yet undescribed allergens. Based on the negative IgE determinations to legumins, vicillins, and conglutins included in the ISAC platform [6] (Ana o 2, Ber e 1, Cor a 9, Cor a 14, Jug r 1, Jug r 2, Sesi 1, Ara h 1, Ara h 2, Ara h 3, Ara h 6, Gly m 5, Gly m 6, and Fag e 2), we suggest that the chia allergens described have no cross-reactivity with these proteins.

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Conflicts of Interest

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Domestic Mites on the Hair/Scalp, Pillows, and Mattresses of Mite-Sensitized Children in a Subtropical Area

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Mites have colonized most ecological systems of the world, including human habitats, where they exist as parasites or live in human dwellings. House dust mites (HDMs) are currently the most common species in indoor environments because the environmental conditions of this habitat have evolved to become drier and cleaner, and skin scales are now the most abundant organic component in domestic dust. HDMs are able to feed on skin scales, an inheritance from their ancestors living in bird nests [1], and therefore have practically no competitors for food in homes [2].

Records of HDMs on skin predate those of HDMs in domestic dust, and the first report was of *Dermatophagoides pteronyssinus* on the skin of individuals with scabies [3]. Since then, different mite species, and particularly HDM species, have been reported on human skin, mainly in patients with dermatitis [4]. It is now generally accepted that mites are simple bystanders that feed on the slough from skin scales [5].

Of particular interest was the discovery of mites on the hair and scalp of asthmatic children in tropical regions [6,7]. The clinical significance of this finding has, however, been questioned [8], since extrapolation of mite numbers to grams of dust overestimates exposure. However, the presence of mites on hair could be important in terms of transfer and contamination of the human environment.

Table. Mite species, Mite Population, and Allergen Levels in Hair/Scalp, Pillow, and Mattress Samples

	Hair (n=43)			Pillow (n=42)			Mattress (n=43)		
	Positive Samples (%)	Geometric mean No. of mites		Positive Samples (%)	Geometric mean No. of mites or µg allergen		Positive Samples (%)	Geometric mean No. of mites or µg allergen	
		per sample	per gram		per sample	per gram		per sample	per gram
Total Mites	81.4	3.87	783.7	92.9	130.5	2020.0	97.7	495.6	864.1
Dermatophagoides pteronyssinus	81.4	3.65	737.9	92.9	103.6	1603.0	95.4	360.6	645.9
Dermatophagoides farinae	2.3	2	714.3	19.1	13.7	199.5	27.9	88.4	200.7
Euroglyphus maynei	7.0	1	131.4	23.8	44.4	515.1	23.3	62.5	114.2
Blomia tropicalis	2.3	1	454.5	14.3	32.0	314.5	32.6	106.6	161.2
Tyrophagus putrescentiae	7.0	1	224.2	7.1	6.2	100.3	9.3	36.4	81.8
Chortoglyphus arcuatus				2.4	11.6	37.7	2.3	883.5	575
Histiostoma feroniarum				2.4	12.1	59.9			
Lepidoglyphus destructor							4.7	9.7	82.4
Suidasia reticulata							4.7	38.9	47.9
Carpoglyphus sp.							2.3	14.1	32
Cheyletus spp.	2.3	1	61	9.5	12.5	78.4	32.6	41.2	58.7
Tarsonemus spp.				4.8	33.7	73.6	14.0	56.9	104.8
Prostigmata				2.4	4.3	47.8			
Oribatida				2.4	32.7	54.3	2.3	304.6	328.4
Mesostigmata							4.7	12.2	32
Der p 1				100	1.6	15.2	100	7.9	13.5
Der f 1				96.6	1.1	8.0	82.9	3.3	8.1

The objectives of this study were to evaluate the presence of mites on the hair/scalp of mite-allergic children and to determine the correlation with the mite population on the children's pillows and mattresses.

Forty-three boys aged 4 to 18 years (mean age, 7.2 years) with positive skin tests to *D pteronyssinus* were selected at the allergy unit of Hospital Dr. Negrín in Las Palmas de Gran Canaria, Spain. All the children had rhinitis and 31 (72.1%) had asthma. None had atopic dermatitis. The study was approved by the ethics committee of the hospital, and informed oral consent was obtained from the children and their parents or legal representatives.

The children's hair was vacuumed for 1 minute with a standard 2000-W vacuum cleaner equipped with a dust trap and a paper filter. The children were asked not to wash their hair for 3 days prior to collection of the samples. Dust samples were collected from pillows and mattresses by vacuuming the entire surface for 1 minute. After collection, the samples were weighed and separated into 50-mg aliquots to determine mites and allergens, following a previously described method [9]. When the weight of the sample was less than 50 mg, the entire sample was used for mite determination. Allergens were quantified using monoclonal antibody kits (Indoor Biotechnologies) according to the manufacturer's instructions. Hair, pillow, and mattress samples were obtained from all children except 1, who had no pillow. Allergens were not evaluated in hair/scalp samples or in 13 pillows due to the small amount of dust collected. The mean (SD) weight (g) of the samples was 0.008 (0.002) for hair/scalp, 0.139 (0.025) for pillows, and 0.822 (0.115) for mattresses.

The results were expressed as µg of allergen or number of mites per *1*) gram of dust or *2*) amount of dust collected in the sample. This second analysis does not extrapolate to grams of dust and reflects the allergen and mite content in the collected sample.

The Spearman rank order test was used to determine the correlation between variables. A *P* value of less than .05 was considered statistically significant.

The Table shows the results obtained. Sixteen mite species were identified. The most frequent species in the 3 habitats was *D pteronyssinus*. Worthy of note was the presence of intact adults and immature forms of *D pteronyssinus* on the hair/scalp and the presence of *Blomia tropicalis* in high numbers on mattresses but not on the hair/scalp.

Positive correlations were found between the number of *D pteronyssinus* on the hair/scalp and on pillows or mattresses. This correlation was significant on pillows when analyzed per sample (r=0.363, *P*=.018) and on mattresses (r=0.441, *P*=.004) when the results were extrapolated to grams of dust. No correlation was found for other mite species (*P*>.05). Positive and significant correlations were found between mite numbers on pillows and mattresses for *D pteronyssinus*, *Dermatophagoides farinae*, and *Euroglyphus maynei* regardless of how the results were expressed (*P*<.05). A positive and significant correlation between mite populations and allergen levels when results were expressed per sample was found on pillows for *D pteronyssinus*-Der p 1 (r=0.567, *P*<.001) and for *D farinae*-Der f 1 (r=0.475, *P*=.032). However, when results were extrapolated to grams, this correlation remained significant only for *D farinae*-Der f 1 (r=0.601, *P*<.001). Hair/scalp mites were not correlated with allergen levels on mattresses or pillows.

Our results confirm that the human hair/scalp is a suitable habitat for dust mites [6,7], and for *Dermatophagoides* species in particular. This may be due to morphological adaptations stemming from the mite's parasitic ancestors [10]. We compared results expressed per gram of dust and per sample, and found the results varied greatly depending on the estimation method used. When the weight of samples is less than 0.5 g, extrapolating results per gram of dust leads to exaggerated estimates of mite and allergen levels [9].

The presence of immature *D pteronyssinus* in hair/scalp samples suggests that the mites were alive when the samples were collected, and the significant association between *D pteronyssinus* on the hair/scalp and on pillows and mattresses indicates that transfer may occur between these surfaces and that hair could act as a reservoir. Other studies have found no correlation between mites on the skin and on bedding [4], but this discrepancy may be due to a closer association between the head and pillows, facilitating the transfer of mites from hair to pillow and vice versa.

In conclusion, our results support the importance of the hair/scalp as a contaminating source of mites. However, its importance as a source of allergens is more difficult to ascertain. Although we did not determine allergens in hair samples, the small quantity of mites suggest low allergen levels, which would confirm previous findings [8]. More studies are needed to verify the clinical significance of these results.

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Conflicts of Interest

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Previous Presentation

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Occupational Asthma in Seafood Manufacturing and Food Allergy to Seafood

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Palabras clave: Asma ocupacional. Metabisulfito sódico. Alergia a mariscos. Calamar.

Fish and seafood are valuable sources of allergenic proteins, and large quantities of fresh and packaged products are consumed worldwide. To preserve nutrients and ensure proper conservation, a number of chemicals such as sodium metabisulphite are used as preservatives and nutrients during manufacture and packaging.

A 38-year-old woman with latex allergy and contact dermatitis to black rubber, carba, and thiuram who had been working as a seafood-packing assistant for 10 years was seen at our clinic. Her duties consisted of handling squid, octopus, shrimp, cod, and catfish while wearing nitrile gloves. These food items were removed from baskets, weighed on scales, and put in iceboxes to which sodium metabisulphite was added as a chemical treatment for conservation. She worked 5 days a week, 8 hours a day, and never used protective clothing or a mask at work.

She had experienced chest tightness, wheezing, and progressive dyspnea during working hours for the previous 3 years; these symptoms improved partially following the use of beclomethasone/formoterol on demand. Her clinical condition improved considerably during vacation time. Over the last 7 years, when she ate shrimp, octopus, squid, or fish, she immediately experienced intense oral pruritus, nausea, abdominal pain, and dizziness, which subsided in a matter of hours without medication. She thus avoided intake of these food products. The physical examination was normal.

Skin tests (prick by prick) with shrimp, octopus, squid, hake, cod, and trout were positive. Specific IgE (ImmunoCAP, Phadia) was positive to octopus (1.63 kU/L), squid (12.8 kU/L), sardines (1.23 kU/L), sole (2.43 kU/L), and latex (8.47 kU/L), and negative to shrimp (<0.35 kU/L) and anisakis (<0.35 kU/L). Baseline spirometry was normal, the bronchodilator test was negative, the baseline fraction of exhaled nitric oxide (FE_{NO}) was 32 ppb, and the baseline methacholine test was positive (concentration required to produce a 20% reduction in forced expiratory volume in the first second [FEV_1] [PC_{20}], 9.5 mg/mL).

After obtaining written informed consent, we performed a specific inhalation challenge (SIC) with sodium metabisulphite in a 7-m^3 chamber in which the patient had to pass the sodium metabisulphite from one tray to another, producing a cloud of

dust. The cumulative exposure time was 30 minutes and the mean concentration of sodium metabisulphite was 1.5 mg/m^3. The concentration of aerosolized particles was measured on a DustTrak Aerosol Monitor (model 8520) (TSI) with a threshold limit value to sodium metabisulphite of 5 mg/m^3. The SIC was positive with a late asthmatic response. Thirteen hours after exposure to sodium metabisulphite, there was a fall in FEV_1 of 17.3% and the patient developed cough and chest tightness. FEV_1 and peak expiratory flow were monitored with a computerized asthma monitor (Amos, Jaeger) every hour except when the patient was sleeping. The methacholine test 24 hours after the SIC was positive (PC_{20}, 1.58 mg/mL), with a decrease of more than 2 concentrations relative to the previous fall. The FE_{NO} 24 hours after the SIC was 27 ppb, showing no significant changes.

On a different day, we performed another SIC simulating the patient's working conditions in a 7-m^3 chamber. The patient was asked to clean and handle raw squid, without sodium metabisulphite, for a cumulative exposure time of 60 minutes. The challenge elicited a late asthmatic response, with a fall in FEV_1 of 12% 10 hours after exposure. At the same time, the patient also developed cough and chest tightness, which were brought under control with salbutamol. The methacholine test performed 24 hours after the SIC with squid was positive (PC_{20}, 0.5 mg/mL), with a significant decrease with respect to the baseline value. There were no changes in FE_{NO}.

Prior to these tests a bronchial challenge with placebo (lactose) was performed, with monitoring of FEV_1 over 24 hours using the same technique as above; no changes were observed. The whole study was performed over the course of 8 weeks, during the patient's sick leave.

We have reported a case of occupational asthma to sodium metabisulphite and other seafood products (cephalopods, fish, and crustaceans) in conjunction with food allergy to these foods. Asthma was demonstrated by SICs and variations in nonspecific airway hyperresponsiveness.

Only a few cases of asthma induced by sodium metabisulphite have been reported to date, namely in the fish-processing industry [1] and in radiographers [2]. This is the first case to be reported in Spain. Occupational asthma in the fish and seafood industry is well known [3,4], but no cases have been reported to date with double sensitization to sodium metabisulphite and seafood allergens.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Occupational Asthma and Eosinophilic Esophagitis in a Patient With Egg-Bird Syndrome

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Palabras clave: Síndrome ave-huevo. Esofagitis eosinofílica ocupacional. Asma ocupacional. Gal d 5.

A 39-year-old nonsmoking woman who had been working as a daycare cook for 15 years reported a history of egg allergy since childhood. When she ingested egg as a hidden allergen she experienced oropharyngeal pruritus, vomiting, diarrhea, dyspnea, and dysphagia. Fifteen years ago, she had similar symptoms when she ate chicken but she now tolerates this meat and other poultry. She has had perennial asthma for 20 years; on one occasion, she had an asthma attack after being in a dovecote. She has experienced dysphagia and food impactions in the last 7 years. She told us that a year earlier she had experienced dry cough and breathlessness when cooking raw egg at work. Furthermore, when cooking chicken, she had mild symptoms of asthma.

After 2 months of treatment with omeprazole 40 mg, we requested an upper endoscopy with sectional biopsies of the esophagus, stomach, and duodenum, which showed over 25 eosinophils per high power field (Eos/HPF) in the 3 sections of the esophagus. The stomach and duodenum were normal.

Eosinophilic esophagitis (EoE) was diagnosed, and an egg- and poultry-free diet was prescribed. At 6 weeks, we conducted a second endoscopy and observed that the eosinophils had disappeared in the 3 sections of the esophagus.

After the second endoscopy, the patient ate rice with chicken and immediately developed oral allergy syndrome, dysphagia, coughing, choking, nausea, vomiting, and colicky abdominal pain that required emergency care. In just a month and a half, she had lost tolerance to chicken.

The patient was asked to perform peak flow measurements before and after cooking egg and her records showed values ranging from 40% to 50%. She subsequently began to experience dysphagia and the sensation of a lump in her neck. We repeated the endoscopy, taking biopsies of the 3 sections of the esophagus, each of which had over 15 Eos/HPF.

On reviewing the history, we observed that the patient had adhered to the diet during vacation time (2012), and had therefore not been exposed to egg. After returning to work the EoE was reactivated, suggesting an occupational origin. The same examination was repeated after vacations (2013) and no eosinophils were detected in the esophagus.

An allergy study showed positive skin tests (mean wheal in mm) to *Dermatophagoides pteronyssinus* (3 mm), egg white (7 mm), egg yolk (10 mm), and chicken (5.5 mm). Skin prick tests to lipid transfer protein, profilin, epithelia, pollens, fungi, and mites gave negative results. Specific IgE (InmunoCAP, Phadia) was positive to egg white (5.83 kU/L), egg yolk (31.3 kU/L), feathers (1.96 kU/L), and chicken (1.30 kU/L). Negative results were obtained with cow's milk, cereals, nuts, legumes, fish and shellfish, pollens, fungi, mites, and epithelia. The chest x-ray and spirometry were normal (forced expiratory volume [FEV] in the first second, 3.24; forced vital capacity, 3.74; peak expiratory flow, 7.21; FEV_{25-75}, 3.78). A methacholine test using the abbreviated cumulative method was positive with a cumulative dose of 0.682 mg.

The literature describes extensively the association between respiratory allergy to bird allergens and food allergy due to ingestion of egg yolk [1,2]. Patients with this syndrome are sensitized to egg protein of avian origin (feathers, bird droppings, and sera) [2]. RAST-inhibition studies have described livetin (water soluble fraction of yolk proteins) as the allergen responsible for cross-reactivity between poultry and egg yolk proteins [3]. Subsequently, it was found that there are common allergens in the feathers of parakeet and hen, hen serum, and alpha-livetin (chicken serum albumin [CSA]), indicating that this protein was the offending allergen [4]. This was later corroborated in a study of 8 patients with double sensitization (bird feathers and egg yolk) by Quirce et al [5], who proposed the designation of Gal d 5 for alpha-yolk.

Most often, respiratory symptoms appear first, followed by food allergy to egg yolk. However, prior allergy to yolk may sometimes predispose to respiratory symptoms caused by exposure to birds [5]; our patient belongs to this subgroup, since she was first allergic to egg and later developed asthma. Based on the order of appearance of the symptoms, the syndrome would be classified as egg-bird syndrome, which is more common in adults and women, but has also been described in children [6].

This case highlights the systemic involvement of allergic disease. Our patient probably developed allergy to chicken meat years ago when she began to experience oropharyngeal pruritus; by continuing to ingest this meat, however, she was probably spontaneously desensitized and able to tolerate chicken for years. When she stopped eating poultry, she lost tolerance, with symptoms appearing later [6-7]. If our patient had stopped eating poultry and if she had not been a cook, she might not have developed EoE, since by prohibiting the consumption of chicken and removing exposure to the allergen while on vacation, we induced clinical and pathological remission [8-9]. Remission of EoE during vacations (twice) and reactivation at work indicate an occupational origin.

The allergen (CSA) triggered the EoE first through the digestive tract and then by inhalation [10].

A detailed history including information on the patient's habitat, hobbies, and occupation is crucial for the etiological diagnosis of bronchial asthma and must be performed before the asthma is categorized as nonallergic and once the causal allergen has been identified; it is also important to consider the possibility of cross-reactivity. Therefore, in our patient, although the allergen responsible for asthma has always been the same (CSA), at first the source was birds, but now, due to her profession, it is chicken egg [5].

We have reported the first case in the literature in which a patient with egg-bird syndrome developed asthma (inhaled egg) and occupational EoE due to allergy to Gal d 5 or CSA (due to ingestion of poultry and subsequently inhalation of egg proteins when handling egg). In addition, EoE was reactivated through the digestive tract and through inhalation.

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Angiotensin Receptor Blocker–Induced Visceral Angioedema

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Key words: Visceral angioedema. Angiotensin receptor blocker.

Palabras clave: Angioedema visceral. Bloqueador del receptor de la angiotensina.

Angioedema is a rare complication of angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) therapy. In a large study of more than 2 million patients on antihypertensive therapy, the cumulative incidences per 1000 persons were 1.79 cases for ACEIs and 0.62 cases for ARBs [1]. The risk of recurrent angioedema with ARBs for patients with previous ACEI-associated angioedema is 6.6% [2,3]. Isolated visceral angioedema has not been previously reported with ARB treatment after discontinuation of ACEI.

A 31-year-old African-American woman with a history of chronic abdominal pain, hemodialysis-dependent end-stage renal disease, and hypertension presented to the emergency department with a recurrent bout of severe abdominal pain, nausea, vomiting, and diarrhea. The patient's current medications included nifedipine, losartan, and clonidine. Physical exam revealed tenderness in the epigastrium and right lower quadrant, and hypoactive bowel sounds, without guarding or rigidity. Complete blood count, a comprehensive metabolic panel, and lipase were normal. Previous noncontrast abdominal computed tomography (CT) scans were remarkable only for perihepatic fluid. In the emergency department, an abdominal CT scan with contrast was performed and revealed perihepatic fluid, as well as small-bowel wall edema and a target sign (stratified appearance of the bowel wall) (Figure). C1-esterase inhibitor (quantity and function) and C4 levels were normal.

Review of the patient's medical records showed that the onset of abdominal pain 6 years earlier had coincided with the introduction of lisinopril. One year ago, the patient also developed a cough which led to discontinuation of lisinopril treatment. She was started on losartan, with resolution of cough but persistence of abdominal pain. Given her current clinical and radiographic findings drug-induced visceral angioedema was suspected. Losartan was discontinued and the patient's abdominal symptoms resolved. At the 12-month follow up, she remained symptom-free off losartan (and all other ARBs and ACEIs), which supported the diagnosis of ACEI and ARB-induced visceral angioedema.

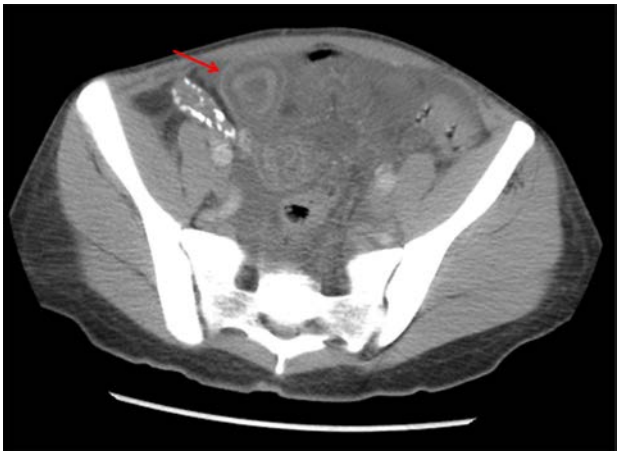

Figure. Computed tomography scan with intravenous contrast of the abdomen and pelvis. Small bowel target sign due to mural stratification and prominent circumferential edema of the bowel wall.

In a study of patients with ACEI abdominal visceral angioedema, CT findings included ascites and small-bowel wall thickening, dilatation without obstruction, and straightening [4]. While ACEI-induced small-bowel angioedema is included in the differential diagnosis of abdominal pain in the setting of current ACEI use, this case report underscores the need to consider intestinal angioedema as a cause of abdominal pain in patients on ARB therapy who present with abdominal complaints.

While the mechanism of ARB-induced angioedema is unknown, mechanisms studied in ACEI-induced angioedema include elevations of bradykinin, substance P, and the bradykinin metabolite, des–Arg9–BK [5]. An accurate medication history will help to differentiate ACEI-induced visceral angioedema from other causes of angioedema. In patients with a history of ACEI-induced angioedema who relapsed following discontinuation of ACEI, the majority (88%) relapsed within a month of stopping ACEI [6]. There have been 28 reported cases of ACEI-induced visceral angioedema in the literature [7]. Given our patient's previous reaction to the ACEI (lisinopril) and persistent abdominal pain for an additional year after discontinuation of lisinopril, losartan was suspected as the causative agent of her current symptoms. The CT scan findings and resolution of symptoms with prompt ARB discontinuation confirmed our clinical suspicion of ABR-induced visceral angioedema.

In conclusion, visceral angioedema of the intestine due to ARBs should be considered in the differential diagnosis of abdominal pain. While there is no definitive diagnostic test for ACEI- or ARB-induced visceral angioedema, the combination of appropriate clinical and medication history, radiologic imaging, and relief of symptoms with discontinuation of the offending medication are helpful in making the correct diagnosis and preventing future morbidity and mortality for these patients.

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Conflicts of Interest

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Occupational Asthma and Dermatitis Induced by Eugenol in a Cleaner

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Key words: Eugenol. Occupational asthma. Dermatitis. Cleaner.

Palabras clave: Eugenol. Asma profesional. Dermatitis. Limpiadora.

Eugenol, 4 allyl-2-methoxy phenol $C_{10}H_{12}O_2$, is a member of the allylbenzene class of chemical compounds. It is a pale yellow oily liquid extracted from certain essential oils, and clove oil in particular. It is used in perfumes, flavorings, essential oils, and in medicine as a local antiseptic, anesthetic, and ingredient in temporary fillings.

Several adverse reactions have been described for eugenol. Most of these have been allergic contact dermatitis [1], but a small number of urticaria cases have been described [2,3]. There has also been a report of occupational asthma and rhinitis in a hairdresser [4].

We report the case of 34-year-old woman who was working for a cleaning company 2 hours a day from Monday to Saturday. She used a mop spray containing several chemical products including eugenol. One month after starting to use this spray, she developed maculopapular erythema on areas exposed to the spray in addition to cough and dyspnea. After successive exposures, her respiratory and cutaneous symptoms became more intense and immediate, and the skin lesions became more generalized. The symptoms resolved in 1 to 2 hours with the use of antihistamines and bronchodilators and disappeared completely when the patient was off work or on holidays.

In the work-up, general biochemistry, complete blood count, coagulation profile, thyroid function, protein levels, serum immunoglobulins (IgG, IgA, IgM, and IgD), complement levels, and nonorgan-specific antibodies were normal. Total serum IgE was 592.8 IU/L and the baseline serum tryptase level was 6.08 µg/L.

Patch testing with the European standard series and fragrance series was negative. Skin prick testing with a series of common airborne allergens, latex, eugenol 2%, clove, and cinnamon showed positive results for *Artemisia vulgaris* pollen only.

The chest x-ray and forced spirometry were normal and the fractional exhaled nitric oxide test result was negative (6 ppb). A methacholine challenge was positive (dose required to cause a 20% fall in forced expiratory volume in the first second [FEV_1], 0.76 mg/dL).

A specific inhalation challenge with eugenol was performed in a 7-m^3 challenge chamber with 2-minute nebulization of

eugenol at the corresponding dilution [4,5]. A bronchial challenge test was negative at a concentration of 1:10000, with no significant differences observed in FEV_1. However, the same challenge with a concentration of 1:1000 led to a 17% decrease in FEV_1 8 hours later accompanied by dyspnea and cough. Skin lesions consisting of isolated and occasionally confluent erythematous maculopapules measuring 2 to 3 cm appeared on the face, chest, back, and arms 12 hours later.

The late decrease in FEV_1 of above 15% accompanied by respiratory symptoms was considered positive in the bronchial challenge [6], and the patient was diagnosed with occupational asthma and dermatitis due to eugenol and removed from her work.

Despite continuous treatment with antihistamines, bronchodilators, and inhaled corticosteroids, the patient progressed poorly and experienced almost daily wheezing, dyspnea, cough, and skin lesions due to small, continuous environmental exposures (perfumes, fresheners, cleaning products, etc.). The patient required many visits to the emergency room and her symptoms were only brought under control with the addition of 6 mg of deflazacort every 48 hours.

The association between exposure to cleaning products and fragrances and the risk of bronchial asthma has been reported [7]. Cleaners are exposed to a large number of products, most of which have an irritating effect on the skin and mucous membranes that can produce worsening of asthma. Other products such as quaternary ammonium and amine compounds can produce asthma by specific sensitization [8].

Exposure to high concentrations of fragrances is associated with the risk of contact dermatitis without disruption of pulmonary function in certain individuals [9]. Most adverse reactions due to eugenol exposure are contact dermatitis, seen mainly in dental personnel [2], hairdressers, and drugstore workers.

In the current case, the spirometric response and appearance of skin lesions after eugenol exposure strongly suggest that eugenol was the cause of the patient's respiratory and cutaneous symptoms, although the pathogenic mechanism is unknown. This condition can be considered an occupational disease because eugenol is a mop spray component whose use is mandatory at work.

This case highlights the fact that eugenol is a potentially serious problem for patients with hypersensitivity to this substance because it is a widespread agent forming part of fresheners, perfumes, and many other products that can be difficult to avoid.

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Conflicts of Interest

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Allergic Contact Dermatitis From Ethylhexyl Salicylate

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Key words: Ethylhexyl salicylate. Salicylates. Allergic contact dermatitis.

Palabras clave: Etilhexil salicilato. Salicilatos. Dermatitis alérgica de contacto.

Ethylhexyl salicylate, also known as octyl salicylate, octisalate, 2-ethylhexyl salicylate (CAS 118-60-5) is a cosmetic ingredient used as both a UV filter and a fragrance compound. Allergic contact dermatitis from salicylates is uncommon. To date, there have been only 3 reports of allergic contact dermatitis due to ethylhexyl salicylate [1-3] and 1 of cheilitis [4], and none of these were in Spain.

We present the case of a 40-year-old woman with a history of rhinitis and intrinsic bronchial asthma under treatment with nasal budesonide 100 mcg/d, fluticasone propionate spray 250 mcg/d, and salbutamol. Over several summers, the patient had developed erythematous micropapules progressing to microvesicles and vesicles on her back, chest, and abdomen (Figure). The lesions appeared only in the summer months, lasted about 14 days, and needed treatment with antihistamines and corticosteroids. These clinical manifestations seemed to be related to the use of sunscreens. The patient reported having used Isdin extrem cream and Isdin transparent spray in the past year. A skin biopsy of the lesions revealed a dermal hypersensitivity reaction consistent with contact dermatitis.

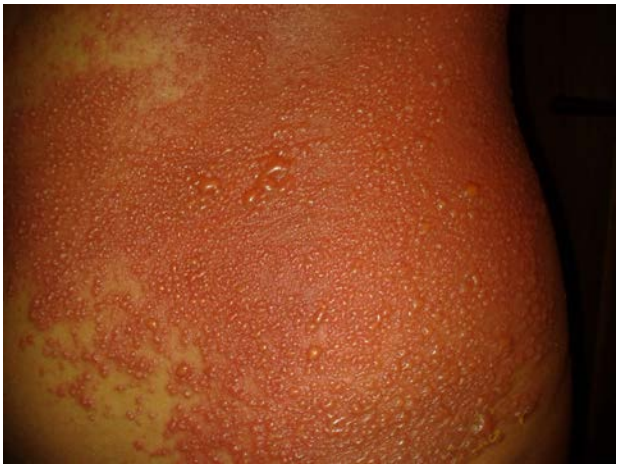

Figure. Skin lesions: papules, microvesicles and vesicles.

Patch testing was negative for Isdin extrem cream and positive for Isdin transparent spray. We performed epicutaneous tests with the components of Isdin transparent spray (supplied by the manufacturer). The whole list of substances was denaturalized alcohol, octocrylene, butyl methoxydibenzoylmethane, ethylhexyl salicylate, C12-15 alkyl benzoate, dibutyladipate, aqua (water), cyclopentasiloxane, 4-methylbenzylidene camphor, diethylhexyl butamido triazone, cyclohexasiloxane, acrylates/ethylhexylacrylamide copolymer, parfum (fragrance), BHT, tocopheryl acetate, and linalool. The results were positive for ethylhexyl salicylate, but negative for the other components tested. Patch tests with a standard patch test series (T.R.U.E TEST, Martitor) gave a positive result for cobalt chloride and a negative result for the rest of contactants included. Patch tests carried out with other salicylates (methyl salicylate, phenyl salicylate, benzyl salicylate, sodium salicylate, salicylic acid, and acetyl salicylic acid, and salicilaldehyde) also showed negative results. Finally, we performed photopatch tests with ethylhexyl salicylate and the other salicylates. The results were positive for ethylhexyl salicylate, with the same intensity as without sun exposure (+++), and negative in all other cases.

Ethylhexyl salicylate has an absorption spectrum ranging from 280 to 320 nm (UV-B). Salicylates are weak UV absorbers, but they are highly water insoluble and therefore suitable for use as sunscreens during bathing. Allergy to sunscreens in the general population is estimated to be less than 2%, but contact dermatitis from salicylates is infrequent, especially considering their extensive use. Thus they represent one of the safest sunscreens, even at high concentrations.

It is noteworthy that the results for other salicylates tested in our patient, including acetyl salicylic acid, were negative. The degree of cross-reactivity between salicylates is currently unknown. In a case of ethylhexyl salicylate allergy reported by Shaw [3], this substance showed cross-reactivity with cis-3-hexenyl salicylate, which has a very similar chemical structure. In another case reported by Mortz et al [1], the patient only showed positive results for ethylhexyl salicylate, despite testing with an extensive series of salicylates. In general, few patients with allergy to a particular salicylate have been patch tested with other salicylates.

Furthermore, there has been a report of contact dermatitis due to methyl salicylate [5] in which oral intake of acetyl salicylic acid produced a recurrence of dermatitis at the site of previous lesions due to methyl salicylate. Our patient tolerated oral acetyl salicylic acid without adverse effects.

In summary, we have reported the first case of contact dermatitis from ethylhexyl salicylate in Spain. Although cross-reactivity between salicylates is unknown, our patient had negative patch tests with other salicylates.

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Conflicts of Interest

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Airborne Contact Dermatitis From *Dittrichia viscosa*

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Key words: Airborne. Contact dermatitis. Compositae. *Dittrichia viscosa*.

Palabras clave: Aerotransportada. Dermatitis de contacto. Compuestas. *Dittrichia viscosa*.

Dittrichia viscosa, previously known as *Inula viscosa*, is an aromatic Mediterranean weed belonging to the Compositae (Asteraceae) family. It grows along roads and pathways and in uncultivated fields, and its lanceolate leaves and stems are covered with fine glandular hairs (trichomes) [1]. *D viscosa* has occasionally been reported as a cause of allergic contact dermatitis [1-3].

A 76-year-old man had experienced a pruriginous erythemato-squamous eruption on his ankles, hands, forearms, and face over the previous 2 years. Sometimes the dermatitis was widespread. The patient related the eruption to trips to the countryside, and in particular to an area where a certain plant grew. The dermatitis appeared exclusively in the months of May to September. The suspicious plant, collected by the patient, was identified by a botanist as *D viscosa*.

Complete blood count, erythrocyte sedimentation rate, and biochemistry were normal. Total IgE was within the normal range (39.7 kU/L). We carried out patch tests with the Spanish standard series (GEIDC), standard commercial pollens, *Chrysanthemum frutescens*, laurel, chamomile, and fresh *D viscosa* plants. Readings were performed on D2 and D4 according to the guidelines of the International Contact Dermatitis Research Group (ICDRG). The only positive result obtained was for *D viscosa* (++ on D2 and D4).

Ethereal extracts from *D viscosa* stems, leaves, and flowers were prepared and used to carry out patch tests at 0.4%, 2%, and 4% in petrolatum (pet). Positive results (++ on D2 and D4) were obtained for all extracts. The same tests were negative in 20 controls.

The main allergens of *D viscosa* are sesquiterpene lactones contained in the leaves and glandular trichomes. The trichomes are released on contact or fall off as the plant withers, leading to an airborne pattern of dermatitis from dry windborne fragments of the plant [1].

Spanish authors Pinedo et al [2] reported the first case of contact dermatitis due to *I viscosa* Aiton in a patient who used the plant in an infusion to treat hemorrhoids. Patch tests were positive with ethereal extracts of *I viscosa* and with 2 sesquiterpene lactones; patch tests with the ICDRG standard series were negative.

Other cases of allergic contact dermatitis to *D viscosa* have subsequently been reported in Portugal [1,3] and there has also been a case caused by *Dittrichia graveolens* [4]. Gonçalo and Gonçalo [1] reported 9 cases of contact dermatitis to *D viscosa*,

mainly with an airborne pattern. All the patients reacted to the fresh leaves and ethereal extracts (1% and 0.5% pet); positive reactions to *Frullania dilatata*, *Laurus nobilis*, other members of the Compositae family, and sesquiterpene lactones were also observed, suggesting sesquiterpene lactone–induced allergic contact dermatitis. Estrela et al [3] reported the case of a patient who experienced dermatitis with an airborne pattern from August to October; patch tests were positive with fresh flowers and leaves, *D viscosa* at 0.5% pet, and alantolactone.

Supporting previous reports, an airborne pattern was also seen in our case. Patch tests were positive with ethereal extracts at 0.4%, 2% and 4% pet and with the unaltered fresh plant. Patch tests with the GEIDC standard series (containing sesquiterpene-lactones) were negative, as in the case reported by Pinedo et al [2], although these authors did observe positive patch tests with lantolactone and isoalantolactone. We did not test lactones other than those included in the GEIDC series (sesquiterpene lactone mix 0.1% pet), but the fact that our patient did not react to other Asteraceae plants suggests that the offending allergen is specific to *Dittrichia* and not a sesquiterpene lactone.

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Conflicts of Interest

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Aspirin Does Not Preferentially Potentiate IgE-Dependent Basophil CD63 Upregulation in Patients With Food-Dependent Exercise-Induced Anaphylaxis

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Key words: Food allergy. Aspirin. Food-dependent exercise-induced anaphylaxis (FDEIA).

Palabras clave: Alergia alimentaria. Aspirina. Anafilaxia inducida por ejercicio dependiente de alimento.

Food-dependent exercise-induced anaphylaxis (FDEIA) is a rare syndrome that was first described in 1979 by Maultiz et al [1], who reported the case of a patient with anaphylactic symptoms after exercise preceded by ingestion of shellfish. Strenuous exercise or ingestion of the causative food alone was well tolerated [1]. In 1983, Kidd et al [2] described 4 patients with similar symptoms and proposed the term FDEIA [2]. In patients with FDEIA for whom challenges with food and exercise are negative, addition of aspirin (as a third potential trigger) or even ingestion of aspirin instead of exercise makes challenge results positive [3,4]. Therefore, aspirin, rather than exercise, is the trigger of anaphylaxis. Aspirin can also stimulate basophils in patients with hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs), although similar results can also be observed in healthy individuals [5]. Since the allergen and aspirin act simultaneously in a patient with FDEIA, it seems interesting to examine the influence of aspirin on IgE-dependent basophil activation.

The study population comprised 7 patients (3 men) aged 26 to 36 years (mean, 29 years) with FDEIA, 17 patients (11 men) aged 31 to 61 years (mean, 42 years) with hypersensitivity to NSAIDs, 17 patients (9 men) aged 21 to 57 years (mean, 32 years) with allergic rhinitis and/or asthma, and 15 healthy persons (8 men) aged 21 to 56 years (mean, 31 years) with no symptoms of allergy and negative skin prick test results (controls). Five of the 7 FDEIA patients had allergic rhinitis and/or asthma; the other 2 had no atopic comorbidities. The number of FDEIA episodes ranged from 1 to more than 10. Symptoms of FDEIA varied from patient to patient and ranged from anaphylactic shock requiring adrenaline to urticaria and itching. Culprit food allergens differed between the patients and comprised celery, carrot, apple, banana, hazelnut, tomato sauce, natural yoghurt, egg, canned ham, and chicken. The intensity of the exercise that triggered the episode was classed as high in 5 patients and mild in 2. Hypersensitivity to aspirin was excluded in healthy persons and patients with allergic

rhinitis and/or asthma. The basophil CD63 upregulation test was performed using the Flow Cast kit (Bühlmann Laboratories AG). Five 50-µL samples of whole blood from each participant were incubated for 20 minutes at 37°C with 50 µL of polyclonal rabbit antihuman IgE (Dako Denmark A/S) at a concentration of 1 µg/mL without aspirin and after adding 50 µL of aspirin (Lys-Aspirin, Bühlmann Laboratories AG) at concentrations of 1.574, 1.13, 0.386, and 0.1 mM, respectively. The aspirin concentrations used in our study were similar to those used in a study by Matsuo et al [6]. After taking 600 mg of aspirin, the plasma concentration yielded peak plasma levels of 28 µM to 56 µM and peak salicylic acid (the main metabolite of aspirin) levels of 72 µM to 290 µM [7]. However, their local concentration in the intestinal tract might be much higher. The activity of IgE-dependent basophils was presented as a percentage of activated basophils after subtracting the patient's background value (spontaneous activity, ie, negative control value). The study design was approved by the Ethics Committee of Wroclaw Medical University, and informed consent was obtained from all the participants.

Aspirin boosted IgE-dependent basophil activation in all the groups, although the increase was not statistically significant ($P>.05$). We noticed various effects depending on the concentration of aspirin. The effect of aspirin on IgE-dependent basophil CD63 upregulation varied from person to person and was not always dose-dependent. Some individuals presented increased CD63 upregulation at lower aspirin concentrations, whereas others did so at higher concentrations, irrespective of the group. Therefore, our results are very disperse, a common finding in nonselected groups.

Our results do not support the observations of Matsuo et al [6], who demonstrated a preferential increase in anti-IgE basophil histamine release in patients with FDEIA or urticaria in comparison with healthy persons. Our findings are more consistent with those of Fukunaga et al [8], who found that ingestion of aspirin by persons with FDEIA changed neither basophil activation nor the results of skin prick tests. In our opinion, the effect of aspirin on IgE-dependent basophil activation in vitro is a rather common feature, and patients with FDEIA do not differ from other individuals in this respect. However, the proposed role of NSAIDs as a nonspecific agent that enhances mast cell and basophil activation by food allergens in the pathogenesis of FDEIA is coherent with current knowledge [6] and seems very likely.

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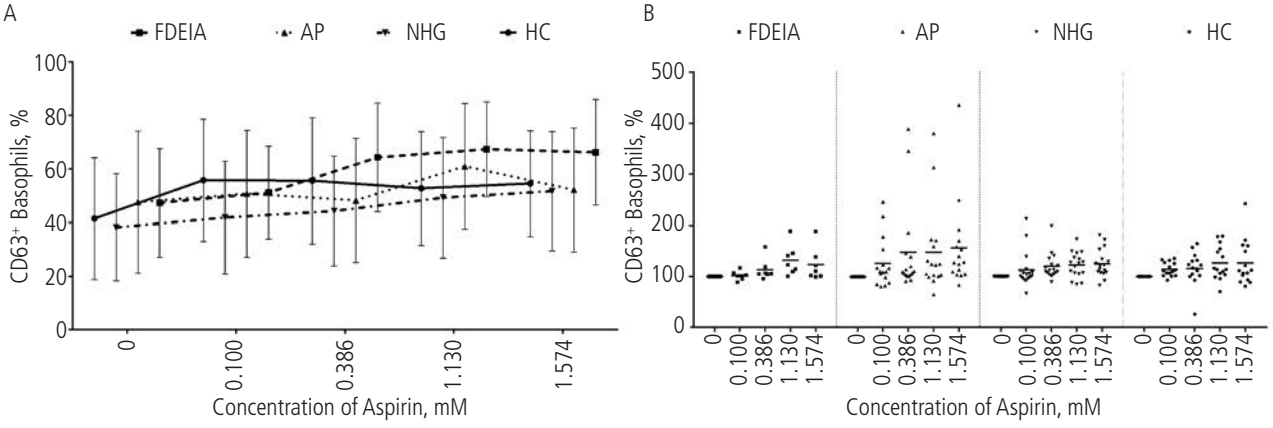

Figure. Effect of aspirin on IgE-dependent basophil CD63 upregulation in patients with food-dependent exercise-induced anaphylaxis (FDEIA), atopic patients (AP), patients with hypersensitivity reaction to nonsteroidal anti-inflammatory drugs (NHG), and healthy controls (HC). A, IgE-dependent CD63 basophil upregulation (shown as percentages of $CD63^+$ cells). B, Increased IgE-dependent basophil CD63 upregulation with increasing aspirin concentrations (shown as the percentage of results obtained without aspirin).

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Marihuana Allergy: Beyond the Joint

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Key words: Basophil activation test. *Cannabis sativa* allergy. Food allergy. Nonspecific lipid transfer proteins. Tobacco allergy.

Palabras clave: Test de activación de basófilos. Alergia a *Cannabis sativa*. Alergia alimentaria. Proteínas de transferencia de lípidos no específicas. Alergia a tabaco.

Plant food allergy is a major health problem. It can be acquired through direct sensitization in the gastrointestinal tract or it can be secondary to a sensitization to cross-reactive pollen or *Hevea* latex [1].

Plant food allergy has distinct geographic and age-related phenotypes. In Belgium, plant food allergy results most frequently from cross-reactivity with birch pollen and is generally characterized by oral allergy syndrome. In the Mediterranean Basin, plant food allergy originates mainly from sensitization to nonspecific lipid transfer proteins (ns-LTPs).

ns-LTPs are panallergens and have been identified as clinically relevant allergenic components in fruits, vegetables, nuts, cereals, pollens, *Hevea* latex, and *Cannabis sativa* [2]. ns-LTPs can show significant IgE cross-reactivity which might lead to various fruit and vegetable allergies, the so-called ns-LTP syndrome [3]. In southern Europe, the ns-LTP of peach (*Prunus persica*) is thought to be an important sensitizing molecule and is frequently used as a marker molecule for ns-LTP allergy. In Belgium, we demonstrated that *C sativa* constitutes a potential source of sensitization towards ns-LTPs and can consequently trigger food allergies [2]. We recently observed an increasing number of marihuana-allergic patients with cross-reactive allergies extending beyond allergy to fruit and vegetables but also involving cereals, *Hevea* latex, tobacco, wine, and beer.

We present our index patient and describe our diagnostic approach with respect to marihuana allergy. A 24-year-old woman attended our clinic in mid-2012 with generalized urticaria, angioedema, and dyspnea after eating cherries, hazelnuts, walnuts, peanuts, nectarines, and apples. Her history disclosed no pollen or latex allergy but revealed that the prior allergic symptoms occurred while smoking marihuana.

In 2013, she consulted because of localized urticaria after using latex gloves and episodes of angioedema and dyspnea after smoking tobacco. She also reported generalized urticaria after eating tomatoes, pineapple, cucumber, raspberries, and fennel and after drinking wine and gastrointestinal symptoms after eating wheat-containing products.

In 2012, we performed skin prick tests (SPTs) as described elsewhere [2], and the result was positive for *C sativa* extract. SPTs with inhalant allergens including fungi and latex disclosed only sensitization to weed pollen. Prick-prick tests with food extracts revealed skin reactivity to apple, peanut, and hazelnut.

SPTs were repeated in 2013 and revealed de novo sensitization to latex and to birch pollen. The result of a prick-prick test with tobacco was also positive.

In 2012, sIgE reactivity was observed to peanut, hazelnut, peach, and tomato, as well as to birch, grass, and weed pollen extracts, but not to latex. Component-resolved diagnosis (CRD) revealed no sIgE to the recombinant components of the pollen allergens, suggesting that the plant food allergy was not caused by pollen or latex. CRD disclosed that the patient was sensitized to cross-reactive carbohydrate determinants and to the recombinant ns-LTP of peanut (rAra h 9), hazelnut (rCor a 8), peach (rPru p 3), and apple (rMal d 3) and to the native ns-LTP of mugwort (nArt v 3).

Determination of sIgE revealed that the patient produced antibodies to the industrial hemp variety of *C sativa* but not to the thaumatin-like protein of kiwifruit (*Actinidia deliciosa*, nAct d 2), thus making sensitization to the thaumatin-like protein of cannabis unlikely [4]. The results of sIgE testing for molds and fungi remained negative.

In 2013, determination of sIgE revealed seroconversion to native *Hevea* latex extract, whereas sIgE to rHev b 1, rHev b 3, rHev b 5, rHev b 6.01, rHev b 6.02, rHev b 8, rHev b 9, and rHev b 11 remained negative. The patient also had a positive sIgE result to tobacco and to the ns-LTP of wheat (rTri a 14).

The Figure shows upregulation of the activation marker CD63 for the ns-LTPs of *C sativa* and peach. In 2013, the result of a basophil activation test (BAT) became positive for the ns-LTPs of tobacco and crude latex extract (data not shown). However, although the patient had no history of kiwifruit allergy and determination of sIgE revealed a positive sIgE to kiwifruit (5.47 kU_A/L) with negative sIgE to various kiwifruit components, BAT with kiwifruit ns-LTP revealed a dose-response shift compared with the other ns-LTP extracts.

We report the case of a 24-year-old woman with an IgE-mediated allergy to marihuana who subsequently developed extensive cross-reactivity to vegetables, fruit, wheat, tobacco, latex, and wine. Diagnosis of cannabis allergy was confirmed by BAT, SPT, and sIgE to industrial hemp, as described elsewhere [2]. Extensive CRD showed these allergies to be part of an "ns-LTP syndrome", with primary sensitization to

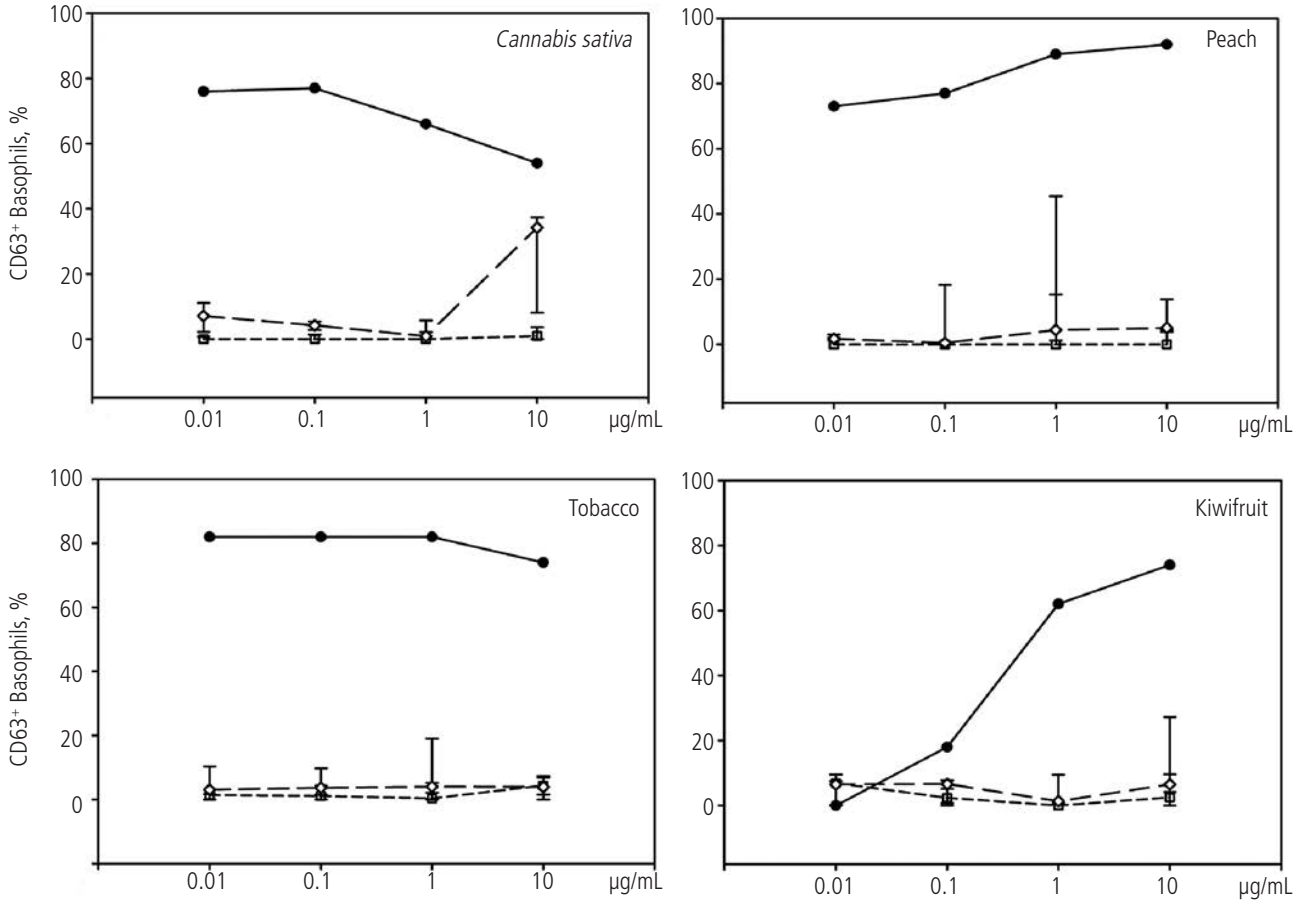

Figure. Percentages of CD63+of the patient's basophils after stimulation with 4 different concentrations of ns-LTP extract from *Cannabis sativa*, peach, tobacco, and kiwifruit (black lines). Median (minimum-maximum) of 3 patients sensitized to the major component of birch pollen, Bet v 1 (long dashes), and 3 healthy individuals who served as controls (short dashes).

Can s 3 from *C sativa*. It has been speculated that Can s 3 is the major allergen of *C sativa* and a potential primary source of sensitization to cross-reactive ns-LTP [5]. Our case-control study revealed that most patients with cannabis allergy are sensitized to ns-LTPs from several sources [2]. Comparison of our data with findings from Spanish surveys [4,5] and US surveys [6] reveals that marihuana allergy and related allergies might differ depending on the geographic region. In the Spanish series, in addition to sensitization to Can s 3, a thaumatin-like protein was found to be another cause of cross-reactivity with food. In contrast to European patients, US patients are rarely sensitized to Can s 3 and do not demonstrate overt food allergy. These distinct sensitization profiles could also be associated with differences in allergen composition, drug manufacturing, and/or sensitization route(s).

In the present case report, different eliciting plant foods are mentioned and many of them have been reported to contain clinically relevant ns-LTPs. However, the potential clinical relevance of tobacco ns-LTP [7] and Hev b 12 from *Hevea* latex [8,9] is unclear.

IgE-mediated reactions to tobacco have been reported, although no association with ns-LTPs has ever been suggested. Stockli and Bircher [7] described a patient who was sensitized to tobacco and cannabis; however, they assumed that the allergic symptoms observed were due to cosensitization.

In conclusion, we report the case of a patient with genuine marihuana allergy and extensive cross-allergies. These cross-allergies are rapidly evolving and have extended beyond fruit and vegetables to involve wheat, tobacco, and *Hevea* latex. As this cross-reactivity appears to be associated with sensitization to an ns-LTP from cannabis, the term *marihuana connection* is proposed.

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Prevalence of Asthma and Related Symptoms in Adolescents: Findings From 3 Surveys

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Key words: Asthma. Adolescents. Prevalence. Severe asthma. ISAAC.

Palabras clave: Asma. Adolescentes. Prevalencia. Asma severa. ISAAC.

The prevalence of asthma has increased significantly since the publication of the International Study of Asthma and Allergies in Childhood (ISAAC) [1]. This standardized and universally validated instrument can be used throughout the world to compare rates between centers within the same country and within the same center on different occasions [1]. Before the advent of ISAAC, few studies had assessed temporal trends in the prevalence of asthma in children. Hansen et al [2] observed that the prevalence of asthma and allergic diseases in Norwegian children (7-14 years) increased over a period of 23 years (1985-2008) [2]. Malik et al [3] studied children (9-12 years) in Aberdeen (United Kingdom) over a longer period (1964-2009) and found a significant increase in prevalence from 24.3% in 1999 to 28.4% in 2004, followed by a decrease to 22.1% in 2009 [3].

In Brazil, the only data available on the sequential prevalence of asthma are those obtained from the ISAAC protocol in adolescents (13-14 years) in phases 1 (ISF1, 1994) and 3 (ISF3, 2003) in 5 centers (Porto Alegre, Curitiba, São Paulo, Salvador, and Recife). In this first reassessment (ISF3), a downward trend in the mean prevalence of current asthma was documented (wheezing in the last year, 27.7% vs. 19.9%), with no change in the prevalence of physician-diagnosed asthma or severe asthma (speech disturbance due to wheezing) [4].

Nine years after completion of ISF3, we thought it would be interesting to determine the prevalence of current asthma among adolescents living in those centers that participated in both ISF1 and ISF3. To answer this question, and following the recommendations of the ISAAC protocol [1], we collected new data in Recife, São Paulo, and Curitiba in 2012 with the approval of the local Institutional Review Boards. The data obtained during ISF1 and ISF3 were analyzed and approved by the ISAAC International Data Center, and the 3 centers were recognized as official. Data were collected at each time point in the same schools as in ISF1 and ISF3. We used the chi-square test for trends, and statistical significance was set at $P<.05$.

The prevalence of active asthma remained stable in Curitiba and Recife, but decreased significantly in São Paulo (Table). However, there was a significant increase in the prevalence of physician-diagnosed asthma. The frequency of episodes tended to decrease in 2003, although it rose significantly in 2012 in all centers. Wheezing associated with exercise remained stable in Curitiba and Recife and decreased significantly in São Paulo. A higher prevalence of nocturnal symptoms was documented in all centers. In general, the prevalence of current asthma remained stable with a tendency to decrease, meaning that it had possibly reached a plateau. The prevalence of physician-diagnosed asthma increased at all centers, as did that of atypical symptoms of asthma (nocturnal cough).

Table. Prevalence of Positive Responses to Questions From the Asthma Core Written Questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC)[a]

Question	Curitiba				São Paulo				Recife			
	1994/5	2003	2012	*P*	1994/5	2003	2012	*P*	1994/5	2003	2012	*P*
	N=3008	N=3628	N=3530	Value[b]	N=3008	N=3161	N=2433	Value[b]	N=3086	N=2865	N=1149	Value[b]
Wheezing ever	40.4	40.7	39.8	NS	45.4	44.6	43.7	NS	39.0	37.8	32.9[c]	<.05
Wheezing last year	18.4	18.9	17.6	NS	23.3	18.7	21.3[c]	<.05	19.7	19.1	19.6	NS
Speech disorder	4.6	3.1	4.5[c]	<.05	5.7	2.9	4.4[c]	<.05	4.8	4.1	7.0[d]	<.05
Physician-diagnosed asthma	8.6	9.2	13.1[d]	<.05	10.0	10.4	13.6[d]	<.05	21.0	18.0	22.5¥	<.05
Wheezing with exercise	19.8	19.1	19.9	NS	20.5	17.0	12.1[c]	<.05	20.8	23.0	22.5	NS
Nocturnal cough	30.1	34.7	42.4[d]	<.05	33.0	33.3	45.4[d]	<.05	31.0	37.3	41.0[d]	<.05

Abbreviation: NS, nonsignificant or stable.
[a]Questionnaire completed by adolescents from official ISAAC centers that participated in Phase 1 (1994/5), Phase 3 (2003), and in 2012.
[b]Chi-squared.
[c]Decrease.
[d]Increase.

During the 18 years since ISF1, we found that the Human Development Index (HDI) in Brazil had increased from 0.724 in 1993-4 to 0.807 [5] in 2012. The HDI included all 3 cities. The data are supported by the change observed in gross national income per capita, which increased from US$3040 in 1994 to US$11 630 in 2012 [6]. Although the economic status of Brazil has improved, no association can be established with the changes in prevalence rates observed in the 3 cities.

In the year 2000, asthma began to receive more attention from the health authorities, which extended free medication for severe asthma to patients with mild or moderate asthma [7] from 2005 onward. The creation of care programs for patients with asthma and continuing medical education might explain the increase in medical diagnosis. It is possible that accessibility to specific treatment enabled better control of the disease, as seen in the reduced frequency of severe exacerbations and nonspecific symptoms in some adolescents. With the introduction of guidelines and consensus statements on asthma, knowledge about the disease is more widespread; therefore, the term *asthma* is increasingly used by physicians and patients to replace euphemisms such as bronchitis and tracheobronchitis. Another consequence was the standardization of asthma management, although this was not always based on national or international guidelines. Finally, air pollution and climate changes may have played a role in the reduced prevalence of the disease. Of the 3 participating centers, the monitoring systems in Curitiba and São Paulo detected a significant improvement in air quality [8,9,10].

In conclusion, the prevalence of current asthma throughout the 18-year period reached its peak and then leveled off. Meanwhile, the prevalence of more severe and atypical forms has increased. The explanations for these findings remain unknown, but the results of the present study indicate that the therapeutic approach to patients with asthma should be as comprehensive as possible and focus primarily on reducing severity and morbidity.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Simultaneous Oral Mite Anaphylaxis (Pancake syndrome) in a Father and Daughter and a Review of the Literature

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Key words: Pancake syndrome. Oral mite anaphylaxis. Food allergy. House dust mite.

Palabras clave: Síndrome del pancake. Anafilaxia oral por ácaros. Alergia alimentaria. Ácaros del polvo de casa.

Oral mite anaphylaxis (OMA), also known as pancake syndrome, is a condition characterized by (severe) allergic reactions after ingestion of food containing mite-contaminated flour. We report for the first time a case of OMA occurring simultaneously in a father and daughter that was probably caused by mite-contaminated beignet flour.

Table. Laboratory and Skin Test Results

Parameter	Patient 1	Patient 2	Normal Value
Total and Specific IgE			
Total IgE	361.7	235.6	<120 kU/L
Dermatophagoides pteronyssinus	76	24.00	<0.35 kU_A/L
Der p 1	49.90	6.62	<0.35 kU_A/L
Der p 2	41.20	11.80	<0.35 kU_A/L
Der p 10	<0.35	<0.35	<0.35 kU_A/L
Dermatophagoides farinae	56.40	12.80	<0.35 kU_A/L
Acarus siroa	3.57	0.52	<0.35 kU_A/L
Glycyphagus domesticus[a]	3.40	1.28	<0.35 kU_A/L
Tyrophagus putrescentiae[a]	12.00	1.56	<0.35 kU_A/L
Wheat	<0.35	<0.35	<0.35 kU_A/L
Buckwheat	<0.35	<0.35	<0.35 kU_A/L
α-Amylase	<0.35	<0.35	<0.35 kU_A/L
Lupine	<0.35	<0.35	<0.35 kU_A/L
Saccharomyces cerevisiae	<0.35	<0.35	<0.35 kU_A/L
Skin Prick Tests[b]			
House dust mite	7/22	5/12	<3/3 mm
Wheat	0/0	0/0	<3/3 mm
Beignet flour (new packet, uncontaminated)	0/0	0/0	<3/3 mm

[a]Storage mites
[b]Skin test results are expressed as wheal/flare reactions in mm.

An 18-year-old girl (patient 1) and her 48-year-old father (patient 2) attended our outpatient clinic because of possible hypersensitivity reactions within 15-30 minutes after ingestion of homemade apple beignets and coffee. Patient 1 experienced dyspnea, generalized pruritus, and eyelid angioedema. Patient 2 presented similar—albeit more severe—symptoms and had generalized urticaria. Both were successfully treated with antihistamines and short-acting β_2-agonists. The clinical history revealed that both patients had an atopic background with rhinoconjunctivitis and mild asthma due to monosensitization to house dust mite. On 1 occasion, patient 2 experienced an identical reaction after ingestion of pancakes made from the same packet of beignet flour, which was stored open at room temperature in a kitchen cupboard. Interestingly, the mother and another daughter, neither of whom was sensitized to house dust mite, had eaten the apple beignets without incident. The table summarizes the laboratory and skin test findings that demonstrate sensitization to house dust mite and various storage mites in both patients. In contrast, no sensitization was observed with wheat, buckwheat, lupine, α-amylase, uncontaminated beignet flour, and yeast. Although the suspected beignet flour was thrown away and therefore unavailable for further testing, we believe these 2 simultaneous case histories and the absence of symptoms in 2 relatives are highly indicative of OMA caused by mite-contaminated beignet flour. Moreover, since the diagnosis of OMA was confirmed, both patients have eaten beignets made from uncontaminated beignet flour such as that applied in the skin tests.

Although the aeroallergens house dust mite and storage mite are well-recognized causes of respiratory allergies such as rhinoconjunctivitis and asthma, their potential as food allergens remains less clear. OMA is a relatively new syndrome, which was first described by Erben et al [1] in 1993. It affects patients of all ages and both sexes and manifests with symptoms that vary depending on the site and extent of mast cell/basophil degranulation, which generally occurs within 15-60 minutes of ingestion. Although the clinical course may be self-limiting, most reactions are severe, with angioedema (also of the oropharynx with stridor) and involvement of the upper and lower respiratory tracts (eg, rhinorrhea, nasal itching and/or congestion, dyspnea, wheezing, and chest tightness). Gastrointestinal symptoms frequently complete the clinical picture. Cardiovascular reactions and death are not excluded [2-6]. To date, OMA has not been observed to present as isolated oral allergy syndrome. An association has been proposed between OMA and hypersensitivity to nonsteroidal anti-inflammatory drugs [2,7] or exercise; however, this association was absent in the cases we report and elsewhere [6]. The latter has been designated *dust mite ingestion–associated exercise-induced anaphylaxis* [8]. OMA has also been described after inhaling cooking vapors from a commercial pancake mix contaminated with the house dust mite *Dermatophagoides farinae* [9].

Although most cases have been reported in tropical and subtropical countries, where climatological conditions are favorable for mite growth (high temperature and relative humidity), the findings presented here and in other case reports [9,10] indicate that OMA can also occur in countries with a temperate climate. In these cases, mite infestation should be sought in inappropriate storage conditions at ambient

temperature, as we report here. In fact, packets of opened flour should be stored in sealed containers in the refrigerator or freezer, where conditions are hostile to mite infestation.

The foods predominantly involved in OMA are pancakes (most common), beignets, sponge cakes, pizza, pasta, wheat bread, white sauce, and meat or fish dusted with wheat flour. In Japan, the food most commonly involved in OMA is okonomiyaki mix, whose ingredients contain wheat flour. Takoyaki mix, which is similar to okonomiyaki mix, is the second most prevalent cause of OMA in Japan [6]. The mite species involved are *Dermatophagoides pteronyssinus, D farinae, Blomia tropicalis*, and the storage mites *Lepidoglyphus destructor, Tyrophagus putrescentiae, Thyreophagus entomophagus, Blomia freemani, Suidasia medanensis*, and *Aleuroglyphus ovatus*. All of these species can live indoors if the conditions are favorable. To date, the allergen(s) responsible for OMA remains elusive. As cooked and baked foods are able to trigger symptoms, it has been suggested that heat-stable components such as Der p 2 are involved in the pathogenesis of OMA [2]. The patients reported here are sensitized to both Der p 1 and Der p 2, but not to house dust mite tropomyosin (Der p 10).

The criteria for the diagnosis of OMA are the following: compatible symptoms occurring after ingestion of food prepared with contaminated flour; previous history of rhinitis, asthma, atopic dermatitis, and/or food allergy; demonstration of IgE-mediated sensitization to mite allergens in vivo or in vitro; positive skin test result with the suspect flour; negative skin test result to wheat and to uncontaminated flour; clinical tolerance to food made with uncontaminated wheat flour; and identification of mites or mite allergens in the suspect flour. However, as reported here and elsewhere [6], the culprit food/flour might not always be available for skin testing or microscopic evaluation. The main differential diagnoses are with genuine wheat allergy and wheat-dependent exercise-induced anaphylaxis.

No cure has been found for OMA. Patients who are sensitized to mites should avoid ingestion of mite-infested food. To our knowledge, there are no data on the effects of mite immunotherapy on OMA.

In conclusion, OMA is easily overlooked and may be responsible for anaphylaxis where no obvious cause is identifiable (idiopathic anaphylaxis). Therefore, mites should be considered in patients presenting with mite sensitization and food-induced allergic reactions with no apparent allergy to the ingredients.

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Oral Tolerance Induction With Wheat: A Valid Therapeutic Option in Allergic Patients

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Key words: Wheat allergy. Gluten. Oral tolerance induction. Liver transplant. Food allergy.

Palabras clave: Alergia a trigo. Gluten. Inducción de tolerancia oral. Trasplante hepático. Alergia alimentaria.

Wheat is the most widely consumed cereal in the world. In Europe, the prevalence of wheat allergy in infancy has been estimated to be 0.1% [1].

In the last few years, an increasing number of studies have investigated achievement of tolerance by repeated exposure to a food allergen (especially cow's milk, egg, and peanut), and the results have been encouraging [2].

We report 3 cases of children with persistent wheat allergy who underwent successful oral tolerance induction (OTI).

Patient 1 was an 8-year-old girl who developed generalized urticaria at 17 months of age immediately after ingestion of baby food containing wheat, oats, barley, rye, rice, and corn. She was diagnosed with gluten allergy based on skin prick testing (SPT) and serum specific IgE determination. Since then, she has followed a gluten-free diet.

At 7 years of age, the results of SPT were still positive to gluten (25 mm), ω-5-gliadin (10 mm), wheat (10 mm), oats (5 mm), barley (15 mm), and rye (16 mm), as were those for serum IgE (ImmunoCAP, Phadia) to wheat (>100 kU_A/L), gluten (>100 kU_A/L), rye (>100 kU_A/L), barley (>100 kU_A/L), oats (17.4 kU_A/L), and ω-5-gliadin (1.54 kU_A/L).

Table. Oral Tolerance Induction With Wheat: Induction Phase

Week	Cereal-Containing Food[a]	Dose
1	Cereal baby food	300 mg
2	Cereal baby food	600 mg
3	Cereal baby food	1.2 g
4	Cereal baby food	3.2 g
5	Cereal baby food	7 g
6	Cereal baby food	14 g
7	Marie biscuit	10 g
8	Marie biscuit	20 g
9	Marie biscuit	40 g
10	Marie biscuit	60 g
11	Marie biscuit	80 g
12	Marie biscuit	100 g

[a]Cereal baby food contained 5.5 g of protein/100 g; Marie biscuit contained 6.5 g of protein/100 g.

At this time, OTI with gluten-containing cereals was started. Baby food (Nutriben, Alter Farmacia) containing 5 cereals (wheat, oats, rye, corn, and rice) was initially administered as shown in the Table. The initial dose was 0.3 g of baby food diluted in water. Doses were increased every week. When 14 g was reached, the baby food was substituted with wheat Marie biscuits (Artiach) to maintain palatability. The induction phase was finished once 100 g of biscuit was tolerated, and a daily intake of at least 100 g of wheat was recommended.

During this phase, the patient complained of occasional, mild abdominal pain.

One year later, she developed generalized urticaria induced by exercise 2 hours after eating a sandwich. She was advised to avoid exercise for 4 hours after ingestion of wheat, and she has not presented further reactions.

Tolerance to rye was confirmed by open food challenge 9 months after OTI.

Patient 2 was a 7-year-old boy who experienced vomiting, diarrhea, and eyelid angioedema immediately after eating baby food containing gluten when he was 1 year old. He was diagnosed with allergy to wheat, barley, and rye based on SPT and serum specific IgE determination. Since then, he has followed a gluten-free diet.

He was also allergic to egg and cow's milk.

He had outgrown the egg allergy by 4 years of age. When he was 5 years old, he underwent successful OTI with cow's milk.

At 6 years of age, serum specific IgE was determined to wheat (4.3 kU_A/L), barley (2.3 kU_A/L), oats (<0.35 kU_A/L), and rTri a 19 (<0.35 kU_A/L). The results of SPT were positive to wheat (10 mm), barley (3 mm), and rye (3 mm) and negative for oats and ω-5-gliadin. Open food challenge with oats was then performed with no adverse reactions. Before OTI, the patient underwent open food challenge with wheat. A few minutes after ingestion of 15 g of Marie biscuit, he began to vomit and developed and perioral urticaria.

OTI with wheat was performed as described above (Table).

The patient did not present adverse reactions during the induction phase and has been on maintenance therapy for 10 months with no reported reactions.

Tolerance to rye was confirmed by open food challenge 9 months after OTI.

Patient 3 was a 14-year-old girl who underwent liver transplant when she was 1 year old because of biliary atresia. Since then, she has been taking daily oral tacrolimus and cotrimoxazole 3 times a week. Two years after transplant, she developed multiple food allergies to milk, egg, kiwi, banana, gluten-containing cereals, fish, and tree nuts.

At 13 years of age, the patient underwent an open food challenge with wheat Marie biscuits. After ingesting 2 g (0.13 g of protein), she developed dysphagia and oral pruritus. The results of SPT at that time were positive for gluten (11×10 mm), wheat (15×7 mm), barley (5×5 mm), and rye (5×5 mm) and negative for oats. Serum gluten IgE was 8.67 kU_A/L.

We followed the protocol described above, but the patient eventually rejected the biscuits, so they were substituted with an equivalent amount of wheat bread. During the induction phase she complained of occasional mild abdominal pain and, after 10 weeks, could tolerate 100 g of bread. She has been on maintenance therapy for 4 months with no further reactions.

Tolerance to rye was confirmed by open food challenge 3 months after OTI.

Although patients tend to tolerate wheat allergy, most outgrow it by late childhood or adolescence [3,4]. During this time, an exclusion diet was the only possible therapeutic approach besides medication for accidental exposure. Few reports on OTI with wheat have been published [5-7]. Recently, Rodríguez del Río et al [7] described a short protocol followed by 6 wheat-allergic children with a favorable outcome in 5 cases. This is the most extended report on wheat OTI published up to date.

Gluten, specifically Tri a 19 (a ω-5-gliadin) [8] and Tri a 36 (a low-molecular-weight glutenin) [9], has been identified as a major allergen in immediate wheat allergy in children. Gluten is also present in barley and rye. Oats are gluten-free, although they can be a source of gluten, since many oat products are contaminated with wheat and barley during harvesting and milling processes.

Interestingly, Rodríguez del Río et al [7] could not demonstrate specific IgE to ω-5-gliadin and glutenin in most of the children included in their study, although they did find a high prevalence of sensitization to 3 members of the α-amylase inhibitor family, thus supporting the role of these inhibitors as major allergens. This profile seems likely for patient 2, who did not have specific IgE to gluten or ω-5-gliadin, unlike patients 1 and 3.

Multiple food allergy is a major problem in children after liver transplantation. Oral tacrolimus and young age at the time of the transplant have been described as risk factors for the development of food allergy, which seems to be persistent over time [10]. This is the first report on successful OTI in a liver transplant recipient.

We believe that OTI with wheat is a valid alternative to an exclusion diet in wheat-allergic patients.

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Conflicts of Interest

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IgE-Mediated Anaphylaxis to Ketoprofen: A Case Report

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Key words: Anaphylaxis. IgE-mediated ketoprofen allergy. Tryptase.

Palabras clave: Anafilaxia. Alergia a ketoprofeno mediada por IgE. Triptasa.

The propionic acid derivative ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) that is used both topically and systemically because of its analgesic and anti-inflammatory properties.

It is frequently responsible for contact and photocontact allergic reactions when used topically, with severe and costly adverse reactions [1]. Nonallergic hypersensitivity reactions are also frequent. These have a wide spectrum of clinical presentations and severity, ranging from cutaneous symptoms such as urticaria and/or angioedema to anaphylaxis [2].

Selective immediate hypersensitivity reactions to a single NSAID are less frequent, and an IgE-mediated mechanism is often hypothesized but rarely demonstrated [3]. Nine cases of anaphylaxis to diclofenac were recently reported. Seven patients underwent allergy testing, and 4 had positive skin test results. In 2, a positive result was also obtained with the basophil activation test [4].

We report the case of a 42-year-old woman with chronic spontaneous urticaria treated with cetirizine 10 mg/d. The patient experienced an anaphylactic reaction characterized by generalized urticaria, labial angioedema, vomiting, diarrhea, and hypotension 2 hours after oral administration of ketoprofen 80 mg. She went to the emergency department, where her blood pressure (BP) was 90/70, and was treated immediately with intravenous (IV) chlorphenamine 10 mg, IV ranitidine 50 mg, and IV methylprednisolone 40 mg. A blood sample was taken to detect serum tryptase (ImmunoCAP, Thermo Fisher Scientific). Cutaneous symptoms receded in about 2 hours, and the patient was discharged with a BP of 130/80.

Six weeks later, the patient was referred to the allergy department of the local hospital. She underwent skin prick and intradermal tests with injectable ketoprofen at a maximum concentration of 3 mg/mL (dilution 1:10), and another blood sample was taken to measure baseline serum tryptase (ImmunoCAP). Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively. Intradermal tests with ketoprofen were also performed in 10 healthy controls, who gave their written informed consent. Skin tests were performed and read according to the indications of the European Academy of Allergy and Clinical Immunology [5].

Skin prick tests yielded negative results but the intradermal test with ketoprofen was strongly positive at a concentration of 0.03 mg/mL (mean wheal diameter, 6.5 mm; surrounding flare, 21 mm) while all the controls had negative results. Serum tryptase was 30.30 μg/L during the reaction, although the baseline value was within the normal range (3.61 μg/L).

These data are consistent with a true anaphylactic reaction caused by an IgE-mediated allergy to ketoprofen.

The tests were followed by an oral challenge test with acetaminophen, in which the patient tolerated a cumulative dose of 500 mg.

NSAID hypersensitivity reactions are very common in clinical practice and are often characterized by respiratory or cutaneous symptoms [2]. Anaphylaxis is less frequent, although it has been reported with diclofenac [4], ibuprofen [6], and naproxen [7]. IgE-mediated reactions are rare and are mostly induced by pyrazolones [3].

We report the first case of an IgE-mediated allergy to ketoprofen confirmed by skin tests. In previous reports of anaphylaxis to ibuprofen [6] and naproxen [8], an IgE-mediated reaction was confirmed by skin prick test only for ibuprofen, whereas skin tests with naproxen were negative.

We think the possibility of an IgE-mediated reaction to an NSAID should always be taken into consideration in patients with severe reactions and no clinical history of other NSAID reactions. Therefore, skin testing with the culprit drug should be performed in all single reactions to confirm or rule out an immune-mediated hypersensitivity reaction. Further studies are needed to establish the concentrations for skin tests to ketoprofen (and other NSAIDs) in order to guarantee adequate specificity.

A possible explanation for the 2-hour interval between ingestion and the reaction is that the patient was under treatment with an antihistamine that could have delayed the reaction.

Serum tryptase is a useful marker for confirming the clinical diagnosis of anaphylaxis and should be applied in all emergency departments.

Our findings are limited by the fact that we did not analyze cross-reactivity with other propionic acid derivatives (eg, naproxen and ibuprofen). Moreover, we did not perform challenge tests with nonselective NSAIDs such as salicylic acid derivatives and acetic acid derivatives, because they could have exacerbated the patient's chronic spontaneous urticaria.

Although no standardized protocols have been designed to date, we recommend considering the possibility of IgE-mediated reactions to NSAIDs and performing skin tests to confirm or rule out allergy.

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Two Cases of Cytarabine Syndrome Successfully Resolved by Desensitization

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Palabras clave: Citarabina. Reacción infusional. Desensibilización.

The chemotherapeutic agent cytarabine is effective in the treatment of acute leukemia and lymphoma. Common adverse effects of cytarabine include myelosuppression, gastrointestinal disturbances, neurotoxicity, and an infusion reaction known as cytarabine syndrome. Cytarabine syndrome commonly presents as fever, diaphoresis, myalgia, skin eruptions [1], and, less frequently, hypotension [2]. While its mechanism is unclear, proinflammatory cytokines are believed to mediate in this flu-like syndrome [3]. The clinical signs and symptoms of cytarabine syndrome are similar to those of allergic reactions. Unlike allergic reactions, the symptoms of cytarabine syndrome can occur even on the first exposure to the drug and are mainly associated with the concentration and infusion rate. Slower infusion rates and premedication with corticosteroids, antihistamines, and acetaminophen can prevent most infusion reactions. However, in some patients, severe infusion reactions occur despite intensive premedication, and measures such as desensitization are necessary before treatment can be continued. Desensitization protocols to prevent non–IgE-mediated infusion reactions have been reported in the literature [4,5], but they are relatively uncommon. Here, we report 2 cases of cytarabine syndrome that resolved successfully after desensitization.

A 45-year-old woman diagnosed with precursor B acute lymphoblastic leukemia underwent bone marrow transplantation but experienced a relapse. She took reinduction chemotherapy including high-dose methotrexate and cytarabine (intravenous methotrexate 1.0 g/m^2 on day 1, followed by cytarabine 3.0 g/m^2 twice daily on days 2 and 3). On the second day, 30 minutes after the first cytarabine infusion, she developed fever (38.3ºC), which rose to 40.3ºC despite treatment with acetaminophen 650 mg, and her blood pressure dropped from 113/74 mmHg to 79/46 mmHg. Her vital signs normalized with normal saline and norepinephrine. However, she experienced shivering, headache, chest tightness, shortness of breath, and hypotension within 2 minutes of restarting the infusion. Her symptoms subsided with discontinuation of cytarabine. On day 3, cytarabine was resumed at a slower rate with premedication (acetaminophen 650 mg, chlorpheniramine 4 mg, and hydrocortisone 100 mg). However, dyspnea, chest tightness, headache, and hypotension reappeared, and the infusion was stopped. After a thorough review of the patient's medications, intravenous fluids, and signs and symptoms, it was decided that the most likely diagnosis was cytarabine-induced infusion reaction. In order

Table. Eleven-Step Desensitization Protocol Used in the First Patient

Solution	Dextrose Water (DW)	Concentration, mg/mL	Total Dose in Each Solution, mg	Mixing Procedure
A	200 mL	0.0087	1.788	Solution B 22 mL in DW 200 mL
B	200 mL	0.0878	17.88	Solution C 22 mL in DW 200 mL
C	200 mL	0.886	178.8	Solution D 22 mL in DW 200 mL
D	500 mL	8.94	4470	Cytarabine 4470 mg in DW 500 mL

Step	Solution	Rate, mL/h	Time, min[a]	Dose Administered, mg	Cumulative Dose Infused, mg
1	A	100	20	0.290	0.290
2	A	250	15	0.544	0.834
3	A	500	14.9	1.080	1.914
4	B	100	20	2.927	4.841
5	B	250	15	5.487	10.328
6	B	500	12.5	9.145	19.473
7	C	100	20	29.532	49.005
8	C	250	15	55.372	104.377
9	C	500	12.5	92.286	196.663
10	D	100	20	298.000	494.663
11	D	250	106.7	3975.320	4469.983

[a]Total time required for desensitization was 271.6 minutes.

to continue administering of therapy with cytarabine, we developed a desensitization protocol. Our 11-step protocol consisted of 4 solutions starting with a 1:1000 dilution of the full concentration. Chlorpheniramine 4 mg and hydrocortisone 100 mg were administered 30 minutes before initiation of desensitization (Table). The patient completed the protocol without adverse events and received the full planned dose of cytarabine.

The second patient was a 66-year-old woman who received induction chemotherapy with fludarabine, cytarabine, and idarubicin for acute myeloid leukemia. She experienced fever, chills, and shivering within 1 hour of the cytarabine infusion, although the chemotherapy cycle was completed with occasional acetaminophen and symptomatic treatment. Since her disease had not remitted after the first course of induction chemotherapy, reinduction chemotherapy was administered with the same regimen. However, she presented fever, chills, shivering, and hypotension after 30 minutes of the cytarabine infusion, and it was decided to administer cytarabine through desensitization. The desensitization protocol used was the same as in the first case, and a full therapeutic dose of cytarabine was administered without breakthrough reactions.

Many antineoplastic drugs, including cytarabine, are frequently associated with infusion reactions. Patients who experience severe reactions require prompt assessment and aggressive management because the reactions sometimes lead to serious complications and discontinuation of therapy. The distinction between infusion reactions and hypersensitivity reactions is often obscure. Most infusion reactions are associated with cytokine release rather an allergic component. However, the mechanisms underlying these reactions remain unclear. Cytarabine syndrome has previously been reported in both children [6] and adults [1]. Ek et al [7] reported that pretreatment with corticosteroids decreased the incidence of fever in pediatric patients receiving high-dose cytarabine, and Metz et al [8] suggested a premedication protocol in a patient with cytarabine syndrome. In the cases we report, premedication was ineffective, and safe administration of the planned dose of cytarabine was attained using the desensitization protocol.

Although desensitization is usually indicated in type I hypersensitivity reactions, it can be applied in severe infusion reactions that persist despite premedication and slower infusion rates, such as vancomycin-induced infusion reactions (red man syndrome) [4]. Severe taxane-induced infusion reactions are also candidates for desensitization, and it has been reported that patients experiencing such reactions can be successfully desensitized with the standard 3-solution, 12-step protocol [5]. Although this protocol is widely used, the infusion rate of the initial step of each solution is too slow to guarantee delivery of a sufficient dose for successful desensitization. Priming intravenous lines with a nondrug solution to reduce exposure to hazardous agents also interferes with infusion of small volumes [9]. To complement this limitation, we modified the protocol reported by Castells et al [10] to design a new 4-solution (1:1000, 1:100, 1:10, and 1:1), 11-step desensitization protocol. As the patients developed severe reactions involving hypotension and oxygen

desaturation, we initiated the desensitization protocol with the bag containing the 1:1000 dilution of the full concentration. Every solution in this protocol is administered at 100 mL/h over 20 minutes to overcome the problem of insufficient dose in the initial steps. In the 2 cases we report, the protocol was successfully administered without breakthrough reactions. Desensitization not only prevents discomfort, but also gives patients an opportunity to continue therapy with a clinically useful chemotherapeutic agent. In patients for whom alternatives are less effective or not available, desensitization can be judiciously applied in patients who are intolerant to chemotherapeutic agents such as cytarabine.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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