PRACTITIONER'S CORNER

Pollen-Food Syndrome Involving Allergy to Tiger Nut

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Tiger nut (*Cyperus esculentus*) is a small tuber native to warm and subtropical regions in the Northern Hemisphere. It is known to have been cultivated in ancient Egypt. Nowadays, it is mainly cultivated, at least for commercial purposes, in the Valencian Community of Spain. High in fiber, proteins, and natural sugars, it is consumed dried or as a vegetable milk extracted directly from the tuber. Although tiger nut has been consumed for a long time, very few cases of allergy after its ingestion have been reported [1-3].

We report on 3 patients aged 47, 23, and 15 years (P1, P2, and P3, respectively) with a history of oral pruritus and dysphagia (P1, P2, and P3) and chest tightness (P1) within minutes of eating tiger nut. All the patients also presented adverse reactions to other fruits, namely peach peel (P1), banana, melon, and coconut (P2), and fruits belonging to the rosacea family (P3). Concomitant atopic conditions were seasonal rhinoconjunctivitis (P1, P2, and P3) and seasonal asthma (P2 and P3).

Skin prick tests to commercial extracts from common inhalants and to natural profilin (Pho d 2) and peach extract enriched with Pru p 3 (as a lipid transfer protein [LTP] marker) as 2 of the main panallergens involved in pollen-food syndrome (PFS) were performed. The results are shown in the Table. Prick-by-prick tests with tiger nut showed a positive result (wheal ≥3 mm) in the 3 patients. Tiger nut protein extract (TN) was prepared by homogenization in phosphate-buffered saline, dialyzation, and lyophilization. Specific immunoglobulin E (sIgE) determinations against TN disclosed positive values (>0.35 kU_A/L) for all 3 patients. sIgE against Pru p 3 and against profilin from different pollen were also carried out (see the Table). Serum specific IgE levels were measured in all cases with the enzyme allergosorbent technique (Specific IgE EIA kit, HYTEC HYCOR Biomedical Ltd.). Tiger nut extract was analyzed by sodium dodecyl-polyacrylamide gel electrophoresis (SDS-PAGE) [4], which showed protein bands ranging between 12 and 97 kDa. SDS-PAGE immunoblotting revealed IgE reactivity with proteins ranging from 66 to 28 kDa and a 16-kDa protein with the 3 sera; a 14-kDa protein was also detected with serum from P2 and P3. SDS-PAGE immunoblotting inhibition assays using TN in the solid phase and the main relevant pollen in our environment as inhibitor phases were carried out. They showed complete inhibition of IgE binding when patient serum was preincubated with *Olea europea* and *Platanus acerifolia*, almost complete inhibition with *Lolium perenne* and *Salsola kali*, and no inhibition with *Cupressus arizonica*. Additionally, profilin from *O europea* produced total IgE-binding inhibition of the 16-kDa band. SDS-PAGE immunoblotting inhibition assays were not carried out with peach LTP since only P1 had a positive skin prick test and sIgE, and no IgE reactivity with proteins around 9 to 12 kDa, (possibly suggesting LTP sensitization) had been identified in the immunoblotting results for P1.

PFS, which was originally termed oral allergy syndrome, results from sensitization to panallergens that are common to pollen and edible plant products; it frequently elicits oral symptoms [5]. The panallergens involved in PFS usually comprise pathogenesis-related proteins, profilins, and LTPs [6]. Individual sensitization profiles to these proteins may vary with geographic location and pollen exposure. Patients with PFS usually have a background of pollinosis as the source of cross-reactivity with foods. All the patients with tiger nut allergy described to date [1-3] had seasonal symptoms and were sensitized to pollen. Nevertheless, the possibility of PFS was not assessed.

We have reported 3 cases of allergy to tiger nut in patients allergic to pollen. SDS-PAGE immunoblotting inhibition assays showed pollen as the primary sensitizer. We suggest that, apart from profilin, as partial inhibition with *O europea* pollen was obtained, other unknown panallergens might be involved in the present study. Physicians should consider PFS in pollinic patients with food allergy and attempt to accurately define individual sensitization profiles, as these would be helpful in both risk assessment and dietary recommendations.

Table. Results of the Allergy Study in 3 Patients With Allergy to Tiger Nut

	Patient 1	Patient 2	Patient 3
Skin prick tests, mm			
Pollen			
Grass mixture	12	12	6
Olea europea	10	11	7
Cynodon dactylis	6	12	5
Phragmites communis	0	10	6
Platanus acerifolia	0	11	12
Cupressus arizonica	10	8	9
Artemisia vulgaris	0	5	3
Chenopodium album	0	6	5
Plantago lanceolata	8	5	11
Parietaria judaica	0	10	10
Salsola kali	3	6	13
Other inhalants[a]	Dog, cat	Dog, cat	Dog, *Alternaria alternata*
Profilin	0	10	9
Peach (LTP marker)	5	0	0
Prick-by-prick, mm			
Tiger nut	5	5	4
Saline	0	0	0
Histamine	5	6	5
Specific IgE[b], kU$_A$/L			
Tiger nut	0.4	1.3	1.9
Pru p 3	0.8	<0.35	<0.35
Phl p 12	<0.35	1.2	13.6
Ole e 2	0.4	2.1	15.8
Platanus acerifolia pollen profilin	<0.35	1.6	7.3
Art v 4	<0.35	2.1	16.6
Total IgE	89	235	1147
IgE immunoblotting IgE reactivity protein, kDa	66-28, 16	66-28, 16, 14	66-28, 16, 14

Abbreviations: Ig, immunoglobulin; LTP, lipid transfer protein.
[a]Including dog and cat epithelia, dust mites, and molds.
[b]Specific IgE determinations were carried out using the enzyme allergosorbent test.

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Echinococcus multilocularis Infection in a Patient Treated With Omalizumab

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We report the case of a 63-year-old woman with a 40-year history of severe, persistent uncontrolled asthma. The patient was treated with inhaled corticosteroids (budesonide 2000 mcg/day), long-acting β-agonists, short-acting β-agonists, montelukast, and methylprednisolone (8 mg/d). Lung function tests showed a forced expiratory volume in the first second of 0.58 L (28.4 % of predicted) and a forced vital capacity of 1.21 L (49.7% of predicted). Skin prick tests were positive for dust mites. Total serum immunoglobulin (Ig) E was 142 ng/mL, while peripheral blood eosinophilia was 100/mm3. Despite adhering to current guideline-based standards of therapy, the patient did not achieve control of asthma symptoms and was therefore considered eligible for omalizumab therapy [1]. Before anti-IgE treatment was begun, we carefully considered numerous possible causes in the differential diagnosis, including parasitic infections (*Echinococcus* species IgG and IgM). The patient lived in an *Echinococcus*-endemic area in north-eastern Poland, where 1.2% to 9.6% of red foxes are infected with *Echinococcus multilocularis*. Routine hematological and biochemical profiles, chest radiography, and abdomen ultrasonography were normal.

The patient was treated every 4 weeks with supervised omalizumab injections at a dosage estimated on the basis of her weight and initial IgE level: 2 subcutaneous injections of 150 mg each, every 4 weeks [2].

After 2 years of omalizumab treatment, the patient started experiencing pain in her right intercostal region. An ultrasonogram of her abdomen revealed characteristic echinococcosis lesions in the liver. A computed tomography (CT) scan and serological screening using enzyme-linked immunosorbent assay followed by Western blotting confirmed the presence of *E multilocularis* infection in the liver [3]. Between the start of omalizumab treatment and the discovery of alveolar echinococcosis (AE) in the liver, no increase in blood eosinophil count or any other laboratory abnormalities were observed. Because of the presence of an active parasitic infection, we decided to stop omalizumab treatment [2]. The patient did not agree to surgery and was treated with albendazole (400 mg/d). After 4 months of albendazole treatment, an abdominal CT scan did not show any progression of the liver lesions. Because of the significant effects of omalizumab treatment—improvement in asthma control test score and symptoms, reduction in consumption of oral corticosteroids (methylprednisolone from 8 mg to 4 mg) and rescue medication, and a significant decrease in acute asthma episodes and hospitalizations—as well as worsening of asthma symptoms after anti-IgE treatment discontinuation and stabilization of AE infection, we decided to continue albendazole (400 mg for 14 days, followed by a break for 14 days) and omalizumab treatments. Omalizumab therapy was restarted, and led to a renewed improvement in asthma symptoms.

Four years after the initial diagnosis of liver AE (February 2008 to May 2012), the patient is still being treated with omalizumab and albendazole.

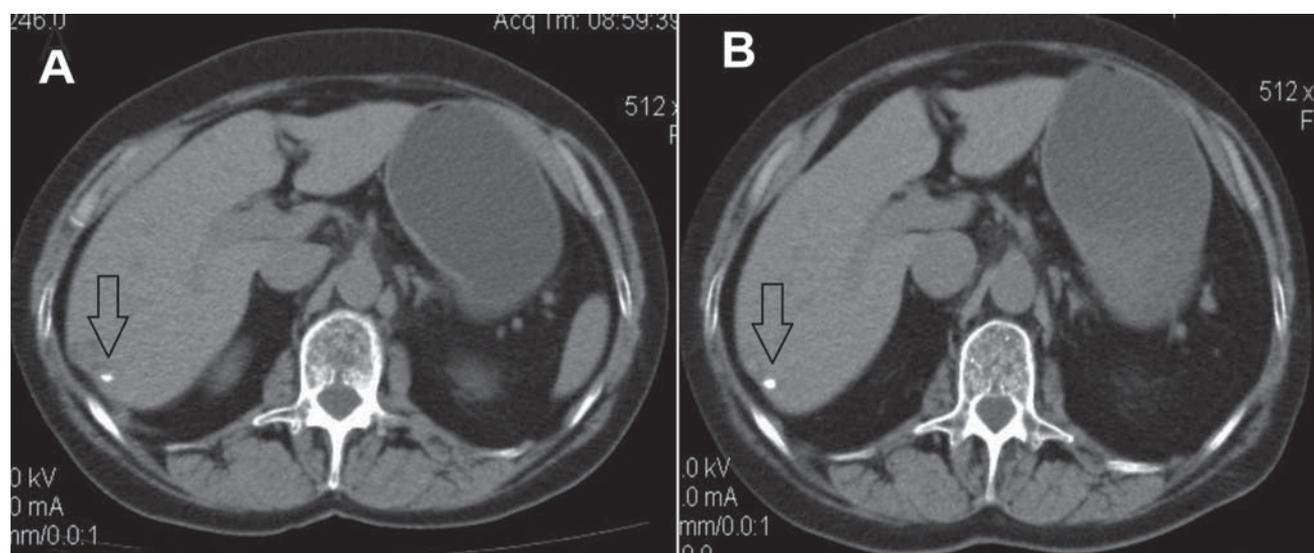Omalizumab is a monoclonal anti-IgE antibody developed

Figure. A, Computed tomography (CT) scan of the abdomen showed hypodense lesions in the liver with calcifications. B, No progression of lesions seen by CT scan 4 months after albendazole treatment.

for the treatment of IgE-mediated diseases, including asthma [2]. Because IgE is also considered to play a central role in protective immunity against some parasites, the use of omalizumab may increase the likelihood of parasitic infections in populations at risk [4]. The mechanisms of protective immunity against parasites are not well understood, but they are generally believed to include changes in intestinal mobility and mucus production, mucosal mastocytosis, and eosinophilia, IgE-mediated activation of mast cells, recruitment of immune effector cells such as type 2 helper (T_h2) cells, eosinophils, and macrophages that lead to the death or immobilization of helminth larvae within eosinophil-rich inflammatory infiltrates [5,6,7].

AE of the liver is a life-threatening disease caused by the intrahepatic growth of the larval cestode *E multilocularis*. Natural mechanisms are able to stop the growth of larvae at the very first stages or after they have started to develop in the liver. An initial acute inflammatory T_h1 response is subverted gradually to a T_h2 response during the chronic phase of AE [8]. Impairment of cellular immunity is typically followed by an increase in susceptibility to *E multilocularis* in experimental animals [9]. Observations in transplanted patients who received immunosuppressive agents have confirmed the increased susceptibility in humans due to impaired immune responsiveness [10].

Because of the presumed role of IgE in helminth infections, it is theoretically possible that omalizumab could increase susceptibility to parasitic infections. Indeed, a randomized, double-blind, placebo-controlled study showed that omalizumab-treated patients experienced more infections when compared with placebo-treated patients [4].

This report provides evidence that, despite the role of IgE in protective immunity against parasitic infections, omalizumab therapy seems to be safe in patients with adequate control of parasite disease. Patients with severe allergic asthma are typically on high systemically active doses of inhaled steroids and some receive oral corticosteroids as well. Omalizumab has been shown to displace the need for oral corticosteroids in these patients. We hypothesize that the improvement of cellular immunity after a reduction in the dose of corticosteroids during omalizumab therapy could enhance resistance to *E multilocularis* infection.

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Safety of 2 Build-up Cluster Immunotherapy Schedules With a High-Dose Hypoallergenic Pollen Therapeutic Extract

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The efficacy of subcutaneous immunotherapy (SCIT) to treat immunoglobulin (Ig)–E mediated rhinoconjunctivitis and bronchial asthma has been clearly demonstrated [1,2].

Cluster SCIT is just a variation of the conventional administration schedule. It involves giving 2 or more series of allergy injections at each visit, usually separated by 30 minutes, to shorten the build-up phase.

Although different cluster schedules are widely considered as adequate alternatives to conventional allergen SCIT [3], since the standardization and quantification of allergen extracts vary among manufactures, safety results are not comparable. Although the efficacy and safety of high-dose hypoallergenic pollen SCIT using a conventional administration schedule have already been shown [4,5], there have been no reports on the safety of these extracts when used in a cluster schedule.

The aim of the present study was to determine whether the use of 2 different cluster schedules of an allergoid with a high concentration of pollinic allergens was a safe and well-tolerated option in patients with pollen allergy.

We performed a multicenter, observational, retrospective study of pollen-allergic patients treated with 2 cluster schedules of SCIT (Allergovit) in 20 Spanish hospitals. Schedule A consisted of 400/400 therapeutic units [TU] on day 1, 1000/2000 TU on day 8, 3000/3000 TU on day 15, and 6000 TU on day 29, while schedule B consisted of 400/400 TU on day 1, 3000/3000 TU on day 8, and 6000 TU on day 22). Allergovit is an aluminum hydroxide-adsorbed depot allergoid preparation of standardized high concentrations of 6 grass pollen allergens modified with formaldehyde. The study was approved by the ethics review board of Hospital Clínico Universitario San Carlos de Madrid.

During the observational period (September 1, 2009 to May 31, 2010), researchers recorded data from patients who met the inclusion criteria (pollinic IgE-mediated rhinitis and/or bronchial asthma) and who, as part of their normal care, were considered for treatment with any of the 2 above-mentioned cluster schedules.

Both the indication of immunotherapy and the assessment of adverse reactions (ARs) were based on the European Academy of Allergy and Clinical Immunology Committee guidelines [6].

Means and SDs were calculated for Gaussian variables and proportions were used for categorical variables. The relationship between variables was studied with bivariate associations. Statistical significance was set a P value of less than .05.

A total of 304 patients were enrolled in the study; 127 (44.1% males and 85% adults) received schedule A (group A) and 177 (49.2% males and 83.1% adults) received schedule B (group B). The mean (SD) age was 28.3 (11.8) and 29.6 (12.3) years for the patients in groups A and B, respectively. The respective prevalence of rhinitis and bronchial asthma was 99.2% and 57.5% in group A and 96.6% and 68.9% in group B.

A total of 839 doses were given with schedule A. There were 72 adverse reactions (ARs) (8.6% of administered doses); 58 of these were local (11 immediate and 47 delayed) and 14 were systemic. Only 32 local ARs (8 immediate and 24 delayed), corresponding to 3.8% of the administered doses, were clinically relevant. The systemic ARs (3 immediate and 11 delayed) were all considered grade 0/1/2 (14%/57%/29%). The most common ARs were urticaria within 30 minutes of the immunotherapy (0.95% of total doses) and bronchial spasm (0.59% of doses). No anaphylactic reactions were recorded. Schedule A was completed in 120 patients (94.4%). Of the remaining 7 patients, a maintenance dose was eventually achieved in 5 patients with slight protocol modifications, and 2 patients did not wish to continue despite the physicians' recommendation to do so.

A total of 901 doses were given in schedule B. There were 78 ARs (8.7% of administered doses); 58 of these were local (19 immediate and 39 delayed) and 20 were systemic. Only 26 local ARs (4 immediate and 22 delayed), corresponding to 2.9% of the administered doses, were clinically relevant. Systemic ARs (5 immediate and 15 delayed), which represented 2.2% of the administered doses, were all considered grade 0/1/2 (25%/65%/10%), and again, delayed urticaria was the most common type of reaction (1.4% of doses). No anaphylactic reactions were recorded. The cluster schedule was completed in 169 patients (95.5%). A maintenance dose was achieved in 5 of the 8 remaining patients with slight modifications to the protocol. Two patients refused to continue with the protocol. Table shows details of the ARs in both groups.

The aim of this study was to assess the safety and tolerance of the normal daily use of common cluster schedules with Allergovit in Spain. We did not wish to reassess the safety and efficacy of Allergovit, as these have already been clearly demonstrated in double-blind placebo-controlled clinical trials [4,5].

Considering the number of patients studied (n=304) and the large proportion of patients who achieved the maintenance dose, we consider that our sample size was large enough to

Table. Local and Systemic Descriptive of Adverse Reactions

	Schedule A[a]		Schedule B[a]	
Local Adverse Reactions				
	No. of Episodes	% of Doses	No. of Episodes	% of Doses
Immediate				
Diameter <3 cm	3	0.35	Diameter <3 cm — 7	0.77
Diameter 3-5 cm	3	0.35	Diameter 3-5 cm — 8	0.89
Diameter >5 cm	5	0.59	Diameter >5 cm — 4	0.44
Total	11	1.29	Total — 19	2.10
Clinically relevant	8	0.94	Clinically relevant — 4	0.44
Delayed				
Diameter <7 cm	23	2.74	Diameter <7 cm — 17	1.89
Diameter 7-10 cm	17	2.02	Diameter 7-10 cm — 5	0.55
Diameter >10 cm	7	0.83	Diameter >10 cm — 17	1.89
Total	47	5.59	Total — 39	4.33
Clinically relevant	24	2.85	Clinically relevant — 22	2.44
Systemic Adverse Reactions				
	No. of Episodes	% of Doses	No. of Episodes	% of Doses
Immediate				
Grade 0	1	0.12	Grade 0 — 1	0.11
Grade 1	2	0.24	Grade 1 — 4	0.44
Clinical description			Clinical description	
Rhinoconjunctivitis	1	0.12	Rhinoconjunctivitis — 3	0.33
Bronchial asthma	2	0.24	Bronchial asthma — 2	0.22
Delayed				
0	1	0.12	0 — 4	0.44
1	6	0.72	1 — 9	1.00
2	4	0.48	2 — 2	0.22
Clinical description			Clinical description	
Urticaria	8	0.95	Urticaria — 13	1.44
Bronchial asthma	3	0.44	Bronchial asthma — 1	0.11
			Rhinoconjunctivitis — 1	0.11

[a]Allergens quantified in the last step prior to allergoidization are 41.66 μg/mL of group 5 in 100% Graminaceae formulation and 18.33 μg/mL of major allergen Ole e 1 in 100% Olea europea formulations.

allow conclusions to be drawn on the safety of cluster schedules with Allergovit.

Bronchial asthma has been reported to be associated with systemic ARs in patients treated with cluster schedules [7]. In our series, although 57.5% of patients with bronchial asthma in group A and 68.9% of those in group B developed systemic ARs, the incidence of systemic ARs did not significantly differ with respect to patients without bronchial asthma. Our results therefore support the idea that if bronchial asthma is correctly stabilized and controlled before initiation of subcutaneous treatment [7], cluster allergen immunotherapy can be safely used.

The degree of skin sensitivity before the start of treatment with hypoallergenic extracts has also been associated with systemic ARs [8,9]. All of the patients in our series had a positive prick test to the allergens included in the therapeutic extract assessed but later assessment of skin reactivity in patients who had experienced a systemic AR did not show any significant differences compared with patients without systemic reactions.

Regardless of the cluster schedule, the most common and significant systemic AR was delayed urticaria (67.8% of the total observed systemic reactions). Unfortunately, we have not been able to identify an explanation for this.

To conclude, we analyzed the safety and tolerance of 2 cluster schedules with a hypoallergenic extract containing a high concentration of major pollinic allergens. In view of the low number of both local and systemic reactions, and their low severity, with a tolerance of around 95%, we conclude that both of the schedules were well tolerated and safe.

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Cardiorespiratory Arrest: A Grade IV Delayed Anaphylactic Reaction in the Recovery Room Caused by Rocuronium

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We report the case of a 71-year-old woman who had undergone 6 surgical interventions, 2 of which were performed in the last 10 years. All of the procedures were performed under general anesthesia, with no allergic reactions.

The patient underwent a mastectomy (breast cancer) under general anesthesia. Two hours after induction, while in the recovery room, she presented a generalized skin rash, wheezing cough, and oxygen desaturation. She experienced cardiorespiratory arrest, and advanced cardiopulmonary resuscitation (cardiac massage, electric shock, and intravenous atropine, norepinephrine, dexchlorpheniramine, and dobutamine) was performed for 10 minutes. An hour later, the patient still had tachycardia, was hypotensive, and presented a generalized rash. She was treated with a 24-hour norepinephrine infusion. As the electrocardiogram showed atrial fibrillation with adequate ventricular response, a 48-hour amiodarone infusion was started, and the patient reverted to sinus rhythm minutes later. Tryptase levels were measured when the inotropic agent was started and 4 hours later. The case was treated as cardiogenic shock rather than pharmacological shock. Blood pressure recovered, and mechanical ventilation and inotropic drugs were suspended within the following 24 hours. Cardiologists ruled out acute myocardial infarction. The echocardiogram showed a normal ejection fraction with no motility disorders.

The first tryptase level, recorded 1 hour after the cardiac arrest, was 59 μg/L. The second tryptase level, recorded 4 hours later was 38.30 μg/L. The reaction experienced by the patient was confirmed to be anaphylactic shock. She attended the allergy service 3 months later. Baseline tryptase value was 5.46 μg/mL. Studies were performed to determine appropriate allergy medications.

In the operating room, the patient was given a dose of amoxicillin-clavulanic acid 2 g, fentanyl 150 mg, propofol 200 mg, rocuronium 50 mg, and ondansetron.

Prick tests with latex, chlorhexidine, povidone, and ondansetron were negative. Prick and intradermal tests with fentanyl, propofol, benzylpenicilloyl polylysine (0.04 mg/mL), sodium benzylpenicilloate (0.5 mg/mL) (DAP-Penicilinas, Diater), penicillin G, amoxicillin, and amoxicillin-clavulanic acid were also negative.

The results of prick tests with neuromuscular blocking agents (NMBAs) were all negative. The result of an intradermal test to rocuronium (0.1 mg/mL) was positive (10×10 mm) within the first 15 minutes and remained positive after 24 hours. Tests for other NMBAs (atracurium and cisatracurium) were also positive (intradermal reaction 8×7 mm and 10×8 mm). However, the patient presented an equivocal reaction to suxamethonium and a negative result with vecuronium.

Total immunoglobulin (Ig) E was 686 kU$_A$/L. No IgE was detected to penicilloyl G, penicilloyl V, amoxicillin, ampicillin, or suxamethonium (ImmunoCAP, Phadia). The results of the basophil activation test (Baso Flow Ex) were negative to amoxicillin, suxamethonium, and vecuronium and positive to rocuronium (22% of activated basophils, cutoff values for drugs ≥5%).

The patient refused a challenge test with amoxicillin-clavulanic acid and was therefore recommended to avoid ß-lactam antibiotics in the future.

Anaphylaxis is an acute, life-threatening systemic reaction that begins as soon as the etiological agent has triggered the reaction. Most of the symptoms appear within the following 60 minutes; however, a delayed reaction (≥1 hour) can occur in a small percentage of cases [1].

The required dosage of resuscitative medications illustrates the severity of the reaction, which varies from grade I (anaphylaxis with generalized signs like erythema, urticaria with or without angioedema) to grade IV (cardiorespiratory arrest) [2].

In this particular case, the signs and symptoms of anaphylaxis were detected 2 hours after the induction of general anesthesia. Grade IV anaphylaxis was confirmed clinically and by the increase in serum tryptase levels. A definite increase in the concentration of serum tryptase (>25 μg/L) suggests an IgE-mediated mechanism [2]. Four hours after the first analysis, tryptase levels decreased, as expected. The baseline tryptase level was 10 times lower than the peak level, consistent with data reported elsewhere [3]. A diagnosis of systemic mastocytosis was ruled out.

Cases of cardiac arrest and death caused by allergy to rocuronium and suxamethonium have been reported within 30 minutes of induction [4]. To our knowledge, the case we report is the only one involving a late anaphylactic reaction that was associated with cardiorespiratory arrest caused by rocuronium.

The potentially increased prevalence of allergic reactions to rocuronium is the subject of debate. The propenyl ammonium groups present in rocuronium and alcuronium might be involved in this apparently increased allergenicity. The risk factor for anaphylaxis in our patient could have been her previous operations; in fact, although she had never been exposed to rocuronium, the operation she underwent 2 years previously was performed with cisatracurium, for which the intradermal test was positive. Cross-sensitization between NMBAs is frequent (affecting between 60% and 70% of

NMBA-allergic patients), but not constant [2]. Cross-reactivity with all NMBAs is unusual, but seems to be more frequent with aminosteroid NMBAs than with benzylisoquinoline-derived NMBAs. Nevertheless, rocuronium belongs to the aminosteroid NMBAs, and cisatracurium and atracurium, the other 2 drugs with positive results in our patient, belong to the benzylisoquinoline-derived NMBAs.

It is essential to perform both in vivo and in vitro testing in patients with suspected allergic reactions, especially in cases of exposure to different medications. In order to diagnose allergy to rocuronium, an objective measure of the allergic response should be obtained by performing skin tests; Leysen et al [5] recommend tests with a positive and negative predictive value of 98% and 96%, respectively. The only drawback of this type of test is the poor standardization in the concentrations used for both the prick and intradermal reactions [5]. The concentration of rocuronium that elicited a positive response in our patient was 100 times lower than that considered nonreactive by guidelines [6]. In vitro studies such as quantification of IgE (not yet commercially available) to rocuronium and the basophil activation test have increased the accuracy of diagnosis, with a positive predictive value of 83% and 97% and a negative predictive value of 72% and 75%, respectively [5].

In reactions such as the one we present, it is necessary to emphasize the importance of serial determination of serum tryptase level to diagnose anaphylaxis and distinguish it from other entities. The basophil activation test and skin testing enabled us to identify an NBMA, vecuronium, that could be administered in the future with a certain degree of safety.

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Urticaria Caused by Ingestion of Pasta and Bread Containing Buckwheat Flour

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Key words: Buckwheat. Soba. Food allergy. Saracen wheat.

Palabras clave: Alforfón. Soba. Alergia alimentaria. Trigo sarraceno.

Buckwheat (*Fagopyrum esculentum*), or Saracen wheat, is a member of the Polygonaceae family. Despite its name, it is taxonomically unrelated to wheat. Buckwheat is frequently ground into dark flour to be used as the main ingredient in several Asian and Russian dishes. In Europe, buckwheat flour is used mostly in regional dishes such as French galettes (a type of crepe from Brittany), Dutch *poffertjes* (small pancakes), Italian *pizzoccheri* (a kind of pasta), and polenta *Taragna* (a hot porridge from northern Italy). Moreover, it is gluten-free and commonly serves as a supplement for patients with celiac disease. Buckwheat can also be a hidden allergen in various foodstuffs. Several cases of buckwheat allergy have been described, although most occur in countries where consumption is common. The prevalence is 3.4% in Japan, 2.9% in Korea, 4.5% in France, and 1% in Italy [1].

We report the case of a 47-year-old woman who was referred to our department after experiencing 2 episodes of acute urticaria. The patient's medical history included allergic rhinoconjunctivitis due to grass pollen that was treated with allergen immunotherapy and winter rhinoconjunctivitis caused by *Cupressus arizonica* pollen. Eighteen months earlier, while the patient was having dinner at a Japanese restaurant, she experienced swelling of the lips, itching of the large skin folds and scalp, and general malaise. The symptoms disappeared without treatment. The patient had eaten noodles with curry sauce for dinner and believed that the noodles were made of soy. However, a meal of soy spaghetti consumed at a later date elicited no symptoms. The patient could not provide the exact composition of the sauce. Some months later, in Russia, immediately after eating 2 types of bread (white and black), she presented itching of the pharynx and large skin folds, which progressed to facial angioedema with generalized urticaria. She received an unknown treatment, and her condition improved immediately. Nonsteroidal anti-inflammatory drugs and other medications were not involved. The patient tolerates legumes, bread, and fruits.

The noodles were identified as soba noodles, which are made from a paste containing buckwheat flour. In Russia, buckwheat flour is often used in the preparation of bread.

The patient provided a sample of black bread from the restaurant in Russia. Extracts were prepared with the bread sample, buckwheat flour, raw soba noodles, and cooked soba noodles (protein content: 10%, 20%, 55%, and 15%, respectively). Skin prick tests, determination of specific serum immunoglobulin E, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), SDS-PAGE immunoblotting, and SDS-PAGE immunoblotting-inhibition were carried out.

General blood biochemistry, complete blood count, coagulation, and levels of basal tryptase were unaltered. Skin prick tests with commercial extracts of pollen (grass, olive, *C arizonica*, *Plantago lanceolata*, and *Artemisia vulgaris*),
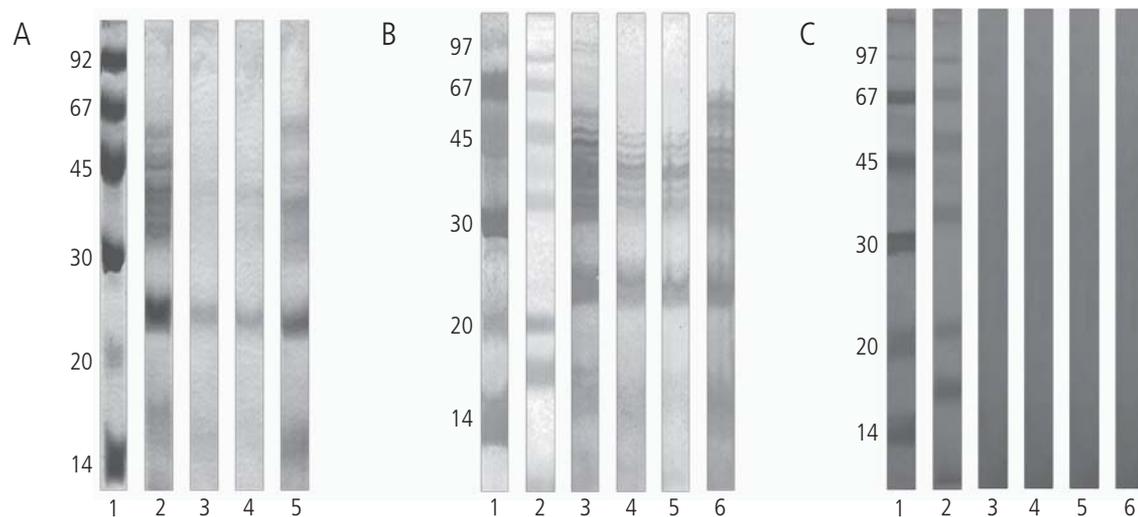

Figure. SDS-PAGE, SDS-PAGE immunoblotting, and immunoblotting-inhibition with buckwheat flour. A, SDS-PAGE. Lane 1, standard; lane 2, buckwheat flour; lane 3, bread sample; lane 4, cooked soba noodles; lane 5, raw soba noodles. B, SDS-PAGE immunoblotting. Lane 1, standard; lane 2, color standard; lane 3, buckwheat flour; lane 4, bread sample; lane 5, cooked soba noodles; lane 6, raw soba noodles. C, Immunoblotting-inhibition with buckwheat flour (1 mg/mL). Lane 1, standard; lane 2, color standard; lane 3, buckwheat flour; lane 4, bread sample; lane 5, cooked soba noodles; lane 6, raw soba noodles.

dog dander, and *Lepidoglyphus destructor* were positive. Skin prick tests with our in-house extracts (10 mg/mL) were positive with black bread (13 mm), buckwheat flour (6 mm), raw soba noodles (15 mm), and cooked soba noodles (15 mm) and negative with white bread.

Total and specific serum IgE levels were assessed using the CAP system (Phadia). Specific IgE was positive to buckwheat flour (21.4 kU$_A$/L), wheat flour (0.36 kU$_A$/L), rye flour (0.46 kU$_A$/L), and soy (0.45 kU$_A$/L). Specific IgE results against nuts and seeds were negative. Total IgE was 236 kU$_A$/L.

The SDS-PAGE and SDS-PAGE immunoblotting performed with extracts of buckwheat flour, black bread, cooked soba, and raw soba revealed similarities in all 4 extracts. Several IgE-binding bands with approximate molecular weights of 24, 16, and 10 kDa were identified in the patient's serum (Figure). These IgE-binding proteins very likely correspond to previously described buckwheat allergens: the 10-kDa and 16-kDa proteins are members of the 2S albumin storage protein family [1-4], and the 24-kDa protein is a member of 13S globulin storage protein family [5-7]. In order to demonstrate the specificity of the IgE bands in the 4 extracts, SDS-PAGE immunoblotting assays were performed with buckwheat flour. Significant inhibition of the bands was observed in the 4 extracts, thus demonstrating that the patient's IgE recognized buckwheat allergens in buckwheat flour, black bread, cooked soba, and raw soba extracts. Therefore, buckwheat flour allergens were present in all 4 extracts.

The patient remained asymptomatic by avoiding buckwheat.

IgE-mediated asthma caused by buckwheat has been reported in Spain [8]; however, to our knowledge, this is the first reported case of an allergic reaction caused by ingestion of buckwheat flour. An IgE-mediated mechanism is suggested in light of the skin prick test and specific IgE results with the implicated foods. Testing revealed several IgE-binding bands, which seem to correspond with the major allergens of buckwheat described to date. It is important to note that migration, globalization, and curiosity about foreign culinary habits, and even interest in reducing costs, should lead us to suspect and discover a broader range of new allergens in the diagnosis of food allergy.

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Chronic Urticaria Caused by Allergy to Peach Lipid Transfer Protein

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Chronic urticaria is characterized by the sudden appearance of wheals with or without angioedema for more than 6 weeks [1]. A large number of studies carried out during the last 2 decades have shown that the disease has an autoimmune or autoreactive origin in about 50% of cases. In the remaining cases, no underlying cause can be identified, and the disease has to be considered idiopathic. Although food allergy is one of the most common causes of acute urticaria, it is generally not considered a possible cause of chronic disease [2]; therefore, routine skin testing for food allergy is not recommended in the workup of a patient with chronic urticaria [2].

We report a case of typical chronic urticaria as a manifestation of immunoglobulin (Ig) E–mediated food allergy.

A 19-year-old boy was recently assessed for a history of recurrent, almost daily, episodes of urticaria/angioedema that had been treated with antihistamines and systemic corticosteroids, often in the emergency department. The family had noted for many years that very severe episodes had sometimes followed the ingestion of aspirin or propionic acid derivatives. Therefore, all nonsteroidal anti-inflammatory drugs (NSAIDs) had been strictly forbidden. When febrile, he took paracetamol, which was well tolerated. The mother had a personal history of respiratory allergy, whereas the patient did not report any respiratory symptoms suggestive of atopy and was unable to associate his urticaria with specific foods. Despite rarely eating fruit and vegetables, he reported good tolerance of banana, watermelon, melon, nuts, carrot, and tomatoes; he normally did not eat Rosaceae fruits. All routine blood measurements (differential blood count, erythrocyte sedimentation rate, C-reactive protein) were normal, as were values for thyroid antibodies, complement fractions, and antinuclear antibodies.

The patient underwent skin prick testing (SPT) with a large panel of commercial respiratory allergens (Allergopharma) and food allergens (ALK-Abelló), following established methods. These showed strong skin reactivity to birch pollen and peach, and weak reactivity to hazelnut and carrot. All remaining respiratory and food allergens, including all other pollens present in this area, mites, molds, animal dander, egg, milk, shrimp, cod, wheat, maize, soybean, walnut, tomato, celery, banana, and *Anisakis simplex* scored negative. The result of an SPT using an extract enriched with commercial date palm pollen profilin (ALK-Abelló) was also negative. In view of these findings, the patient was thoroughly questioned, and it was found that he had drunk commercial peach tea daily for many years. Ingestion of peach tea was stopped immediately, and at the control visit 1 month later the patient reported that he had not experienced any new episodes of urticaria. An open challenge with the commercial peach tea was followed by a recurrence of urticaria, but an SPT with the offending tea showed a weak skin response (mean diameter of the wheal 2 mm, ie, below the minimum size needed to consider an SPT result positive following the criteria of the European Academy of Allergology and Clinical Immunology). Since the commercial peach extract for SPT contains 30 μg/mL of lipid transfer protein (LTP) and lacks both the PR-10 allergen Pru p 1 and profilin (Pru p 4), peach LTP allergy was diagnosed. The weakly positive SPT with carrot was considered most likely secondary to birch pollen hypersensitivity, as the edible part of carrot does not contain LTP [3]. In contrast, since the commercial hazelnut extract for SPT normally scores positive both in birch pollen–allergic patients and in individuals who are allergic to the LTP, it is impossible to say which allergen—Cor a 1 or Cor a 8—caused the weak skin reactivity observed, although the lack of reactivity to walnut [4] suggests that the reactivity to hazelnut was probably a consequence of hypersensitivity to birch pollen. The patient is currently well and tolerates commercial lemon tea of the same brand. He refused to have blood drawn for in vitro tests (ie, measurement of levels of specific IgE to individual peach allergens and of tryptase before and after the elimination diet) and to undergo a challenge with aspirin in order to ascertain the persistence of intolerance to NSAIDs after chronic urticaria had subsided.

Our findings demonstrate that food allergy can sometimes be a cause of chronic urticaria and that specific investigation for food allergy should therefore be carried out on a routine basis, even in patients with a long history of urticaria. The case reported here was characterized by several confounding factors. First, urticaria episodes occurred almost daily, but were not clearly associated with ingestion of the offending food or with cofactors such as exercise. As a consequence, the boy went on drinking commercial peach tea for years, and neither he nor his parents realized that this tea was the cause of his disease. In fact, hypersensitivity to LTP is characterized by extremely variable clinical expression, including contact urticaria, oral allergy syndrome, urticaria, anaphylaxis, or the total absence of symptoms, thus potentially explaining the intermittent clinical symptoms. The reasons for such variability are not understood, but the effect of cofactors such as NSAIDs, exercise, and fasting [5] cannot be ruled out. Second, the patient had a history of urticaria/angioedema induced by different NSAIDs, thus indirectly confirming the hypothetical diagnosis of chronic spontaneous urticaria, as NSAID-induced exacerbations affect about 15% of patients with this underlying clinical condition [6]. Furthermore, IgE-mediated food allergy is generally not the cause of chronic urticaria [2], particularly when it is so long-lasting, although a recent study showed that in certain geographic areas, hypersensitivity to *Anisakis simplex* is associated with chronic urticaria [7]. However, the association between a history of chronic urticaria and intolerance to NSAIDs and hypersensitivity to LTP was recently reported [8], and it is known that aspirin and other NSAIDs can upregulate

type 1 allergic responses to foods, possibly by causing an increase in the permeability of the gut mucosa [9,10].

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High Prevalence of Allergy-Like Respiratory Diseases in Common Variable Immunodeficiency

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Common variable immunodeficiency (CVID) and selective immunoglobulin (Ig) A deficiency (IgAdef) are considered the most common primary antibody immunodeficiencies [1]. In both cases the molecular basis is unknown. CVID involves a profound defect in at least 2 serum Ig isotypes, including IgG, and B cells cannot normally produce specific antibodies against protein and polysaccharide antigens [1]. Consequently, individuals with CVID are more prone to infections by common bacteria and experience general immune dysregulation in the form of autoimmune diseases, lymphoid hyperplasia, granuloma formation, and greater susceptibility to neoplasm than healthy individuals. IgAdef is also associated with a high rate of respiratory, intestinal, and urogenital tract infections, and autoimmunity and collagen vascular diseases are also more common [2]. One of the most intriguing features of IgAdef is the higher prevalence of atopic diseases than in the general population [2]. Since CVID frequently occurs in first-degree relatives of patients with IgAdef, and some patients with IgAdef later develop panhypogammaglobulinemia, both entities have been largely believed to share a common genetic basis [3]. However, little evidence is available on the prevalence of atopic diseases in CVID.

The aim of our study was to retrospectively evaluate the prevalence of noninfectious allergy-like respiratory disease (NIARD) in the form of rhinitis (perennial or seasonal), nasal polyps, or bronchial asthma in a series of adult patients (>20 years) diagnosed with CVID or IgAdef at the Clinical Immunology Unit of the Immunology Department of Hospital General Universitario Gregorio Marañón in Madrid, Spain. All patients were diagnosed according to the criteria of the European Society for Immunodeficiencies. The inclusion criterion was a diagnosis of rhinitis, nasal polyps, or asthma made by an allergist, pulmonologist, or otorhinolaryngologist according to current guidelines [4,5]. The exclusion criteria included fever and/or purulent secretion coexisting with allergy-like symptoms and evidence of granulomatous respiratory disease or bronchiectasis at the time of the NIARD. As a secondary objective, we evaluated the prevalence of other allergy-like and hypersensitivity diseases in patients with CVID and IgAdef.

Table. Clinical Features of Patients With CVID and IgAdef

Parameters	CVID	IgAdef	P Value[a]	Prevalence in the General Population, % [5,6]
No. (women)	31 (17)	28 (15)	0.59	–
Age, y, mean (SD)	49 (18)	43 (13.4)	0.22	–
NIARD, %	41.9	42.9	0.94	–
Rhinitis, %	35.5	32.1	0.78	10-25
Nasal polyps, %	16.1	7.1	0.29	0.5-4.3
Asthma, %	19.4	39.3	0.15	4.5
Chronic urticaria, %	0	14.3	0.045	0.5
Conjunctivitis, %	16.1	28.6	0.35	5-22
Atopic dermatitis, %	3.2	7.1	0.59	2-20
Food allergy, %	3.2	17.9	0.09	1-3
Drug hypersensitivity, %	12.90	0	0.13	7.8
NIARD as first symptom, %	16.1	35.7	0.16	–
Positive SPT (SPTt NIARD), %	0	77.8	0.006	–
Detectable tIgE (tIgEt NIARD), %[b]	25	83.3	0.10	–
Mean (SD) tIgE (tIgEt NIARD)	27 (56)	114 (169)	0.19	–
Autoimmune diseases	38.7	17.9	0.09	–

Abbreviations: CVID, common variable immunodeficiency; Ig, immunoglobulin; IgAdef, selective IgA deficiency; NIARD, noninfectious allergy-like respiratory diseases; SPTt, skin prick test–tested; tIgEt, serum total IgE–tested.
[a]χ^2 test or t test, as indicated, for the comparison CVID/IgAdef.
[b] >2 kU$_A$/L.

The study population comprised 31 patients with CVID and 28 with IgAdef. The clinical features of both groups are presented in the Table. The overall prevalence of NIARD was similar in both groups, as was the distribution of the specific NIARDs (rhinitis, nasal polyps, and asthma). Asthma was more frequent in IgAdef patients, although the difference was not significant. Among CVID patients, 7 out of 13 NIARD patients (53.8%) had undergone skin prick tests (SPT) with aeroallergens that are habitually present in Madrid. All the results were negative. Serum total IgE (tIgE) was measured in 8 out of 13 patients with CVID and a NIARD (61.5%) and was found to be undetectable (<2 kU$_A$/L) in 6 (75%). Of the remaining 2 patients (both SPT-negative), one was a 23-year-old man with seasonal rhinoconjunctivitis and asthma (tIgE, 63 kU$_A$/L) and the other a 79-year-old woman with nasal polyps, asthma, and intolerance to aspirin (tIgE, 150 kU$_A$/L).

As for individuals with IgAdef, 9 out of 12 patients with a NIARD (75%) underwent SPT. Seven (77.8%) had at least 1 positive result in a significantly higher prevalence than individuals with CVID (Table). Serum tIgE was measured in 6 out of 12 patients with IgAdef and a NIARD (50%), all of whom underwent SPT. Of the 2 SPT-negative patients, the one who underwent tIgE testing had an undetectable value (<2 kU$_A$/L). In the remaining 5 patients, mean (SD) tIgE was 136.8 (175.6) kU$_A$/L (median, 71.9 kU$_A$/L), which was higher than the concentration observed in CVID.

Chronic urticaria was only observed in IgAdef patients. Food allergy tended to be more frequent in patients with IgAdef, while drug hypersensitivity tended to be more prevalent in those with CVID. Interestingly, allergic symptoms were detected before the diagnosis of CVID in a subgroup of 16% of patients.

The prevalence of noninfectious rhinitis, nasal polyps, and asthma was higher in our CVID series than in the general population [4-6] and similar to that of IgAdef patients. Since a genetic link between IgAdef and CVID could exist, CVID patients might also be more prone to respiratory atopic diseases. The more profound defect in Ig synthesis seen in patients with CVID could explain the differences in SPT positivity and tIgE value between patients with CVID and patients with IgAdef. On the other hand, STAT6-deficient and IL4-deficient mice with undetectable tIgE have been shown to mount IgE-dependent responses [7], and SPT-negative CVID patients with positive allergen-specific bronchial challenges have been reported [8]. Paradoxically, while the prevalence of allergy-like symptoms was similar in both groups, autoimmune complications were more frequent in CVID, even though both conditions share a B-cell basis. The role of T-cell hypersensitivity or antigen-presenting cell phenomena should be further investigated in this regard. Our study is limited by the small number of patients, the retrospective design, and the absence of an allergology workup (SPT and tIgE) for all the participants. As the association between NIARD and CVID has not been previously suggested, these tests are not systematically performed, thus explaining the lack of data for some patients. In addition, it is not unusual for physicians attending these patients to be unaware of atopic conditions. Our data suggest that the usual diagnostic procedures for

respiratory allergy might be inadequate for individuals with a low Ig titer and dysfunctional Ig, such as CVID patients. A prospective study with a larger number of patients is warranted to confirm our observations. The fact that a subgroup of CVID patients had allergy-like symptoms before diagnosis of CVID is interesting, as a NIARD in the context of recurrent infections/autoimmunity and negative SPT results could suggest humoral immunodeficiency.

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