Late-Onset Food Hypersensitivity to Wheat Flour

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Key words: Recurrent urticaria. Wheat flour. Gliadin. Food hypersensitivity.

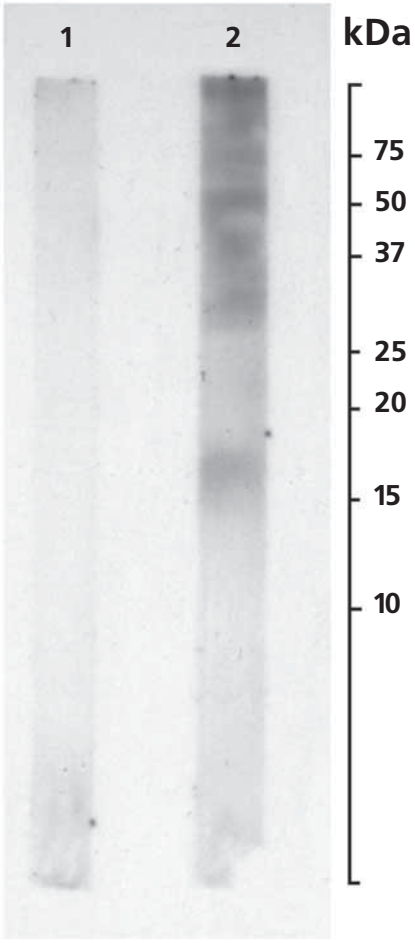
Palabras clave: Urticaria recurrente. Harina de trigo. Gliadina. Alergia a alimentos.

Wheat flour is a known cause of occupational asthma in bakers, whereas wheat-based food hypersensitivity is more frequently described in young patients. Nonetheless, wheat has been recognized as a source of food allergens in adults suffering food-dependent, exercise-induced anaphylaxis. We report a case of food allergy to wheat flour not triggered by exercise in a 60-year-old woman, to the best of our knowledge the oldest patient with this condition reported in the literature.

The patient was referred to our department for evaluation of a 12-month history of episodes of generalized urticaria occurring immediately after meals without associated exercise. The last 2 events also manifested with facial swelling, throat constriction, and dyspnea. The patient had a history of mild seasonal rhinitis but no food allergy. Assessment of dietary intake revealed she had eaten wheat products before every episode.

Skin prick tests (SPTs) were performed with commercially available extracts of common airborne allergens (*Dermatophagoides pteronyssinus; Dermatophagoides farinae; Alternaria* species; cat and dog dander; grass, weeds, *Platanus*, *Olea* and *Cupressus* species pollen; and latex) as well as *Anisakis* species, wheat, barley, corn, rice, rye, soy and gliadin extracts (ALK-Abelló, Madrid, Spain). Total and specific immunoglobulin (Ig) E to house dust mite, wheat, latex and *Anisakis* species were measured by fluorescent-enzyme immunoassay (CAP-FEIA, Pharmacia, Uppsala, Sweden). Sodium dodecyl sulfate polyacrylamide gel electrophoresis IgE immunoblotting was carried out to wheat extract with the patient's serum and a control serum.

SPTs were positive to *D pteronyssinus* (4 × 4 mm), *D farinae* (4 × 5 mm), *Anisakis* species (5 × 5 mm), wheat (5 × 6 mm), and gliadin (6 × 7 mm). Other SPTs were negative. Total IgE was 228.5 U/mL. Specific IgE was detected against *Anisakis* species (13.40 kU/mL, class 3) and wheat (0.87 kU/mL, class 2), but not against house dust mite or latex. IgE immunoblotting to wheat with the patient's serum showed several bands at about 50 and 37 kDa and an isolated band at 17 kDa (figure). The patient was advised to follow a gluten-free diet and a year later she remained asymptomatic.



Sodium dodecyl sulfate polyacrylamide gel electrophoresis immunoglobulin E immunoblotting. Lane 1, negative control; lane 2, patient serum.

In this case of recurrent urticaria and angioedema associated with hypersensitivity to gliadin, a constituent of wheat flour, the patient reacted to house dust mite, which might be a cause of food allergy due to flour contamination; nevertheless, a gluten-free diet proved the diagnosis as outbreaks went into remission. Onset was in the sixth decade of life and the recurrent urticaria and 2 anaphylactic reactions were not exercise-related.

Oral challenge was not performed because a negative result could not rule out food allergy to wheat since an unidentified stimulus might be involved. We believed that an exclusion test would be preferable for diagnosis. Symptoms suggesting celiac disease, which involves different pathogenic mechanisms, were absent and a diagnostic study was not performed for that disorder.

We found an IgE-immunoblotting pattern with high

molecular weight allergens, which probably belong to gluten proteins. Wheat proteins are categorized into 2 fractions according to their solubility in water/salt solutions. The soluble fraction comprises low molecular weight proteins described as the most important allergens in baker's asthma [1] and in children with food allergy [2,3]. Similar soluble allergens are thought to be responsible for symptoms after ingestion or inhalation of other cereal flours at different ages [4]. The insoluble fraction (gluten) is formed by prolamins (gliadins and glutelins) with a higher molecular weight. Gliadin seems to be the major allergen in adult wheat-dependent exercise-induced anaphylaxis [5,6], in some cases of atopic dermatitis [7], and in anaphylaxis in children [8,9]. We conclude that gliadin should be included in the diagnostic work-up for cereal-grain food allergy.

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Attagenus pellio: A Potential Cause of Indoor Allergy

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Key words: *Attagenus pellio*. Dermestidae. Indoor allergy. Persistent rhinoconjunctivitis.

Palabras clave: *Attagenus pellio*. Dermestidae. Alergia de interior. Rinoconjuntivitis persistente.

Intermittent but perennial rhinoconjunctivitis and asthma symptoms are frequent complaints that can be explained in many patients by an allergy to an indoor allergen source. However, finding the relevant allergen is a challenge if no sensitization to common domestic allergens such as house dust mite, pets, or molds can be identified.

We report the case of a 45-year-old woman who experienced recurrent acute attacks of rhinoconjunctivitis and cough during house keeping, particularly when she was cleaning wardrobes. Symptoms occurred exclusively in her own 85-year-old house. One day she noticed larvae and black beetles hidden under clothes (figure). Cleaning the spot, she suddenly felt acute itching in her eyes and nose followed by tearing, sneezing, and coughing. Arriving at our clinic, she showed symptoms consistent with an acute respiratory allergy and ocular chemosis.

Spirometry with flow–volume curve demonstrated slight, partially reversible airway obstruction with a forced expiratory volume in 1 second of 2.3 L (73% of predicted) and 2.7 L (87%) after bronchodilation. The fraction of exhaled nitric oxide (NIOX, Aerocrine AB, Solna, Sweden) was elevated at 81 parts per billion (ppb) (normal < 30

Attagenus pellio beetle and larvae

ppb). Although the eosinophil count in peripheral blood was not elevated, the serum eosinophil cationic protein level was high at 41.8 µg/L (normal, 2.3-16 µg/L). Skin prick tests (SPT) with a panel of common inhalant allergens (Allergopharma, Reinbeck, Germany) demonstrated weak reactivity to house dust mite and cockroach (wheal, 3 mm to both extracts). SPT with the patient's own house dust (1% wt/vol of phosphate-buffered saline [PBS]; pH, 8) elicited a strong positive reaction with a wheal of more than 7 mm. Inspection of the dust revealed the presence of larvae (figure). Similar skin reactivity was obtained with a solution of larvae dissolved in PBS (pH 8) and a prick-to-prick test with living larvae. Two atopic and 3 nonatopic control individuals had no reactions to the solution. In serum, no specific immunoglobulin (Ig) E (ImmunoCAP, Pharmacia, Uppsala, Sweden) to house dust mite, cockroach, moth, or tropomyosin could be detected (class 0, < 0.35 kU/L). However, specific IgE to larvae proteins—identified as *Attagenus pellio*—were found (class 3, 8.5 kU/L) in the patient but not in sera from 5 controls.

Attagenus species belong to the Dermestidae family. Two species are native to Switzerland: *A pellio* and *Attagenus megatoma*. Outdoors, larvae feed on natural materials of animal origin (carcasses, bird nests) and indoors on any animal products or natural fibers. Leather or fur. So far, Dermestidae-related allergy is known as an occupational disease mainly in wool workers or museum personnel [1,2]. A single report of home-related allergic rhinoconjunctivitis and asthma caused by Dermestidae has been published [3].

In conclusion, SPT with crude house dust, although not a standard procedure, may help to identify unknown but relevant indoor allergen sources. Since *A pellio* is common in Europe, otherwise unexplained indoor allergy may be due to these insects.

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Anaphylaxis Due to Lupine Flour in a Celiac Patient

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Key words: Lupine. Anaphylaxis. Peanuts.

Palabras clave: Lupino. Anafilaxia. Cacahuetes.

Lupine (*Lupinus albus*), is a leguminous plant that is widely used as flour or bran in food manufacturing (bread, pasta, baked products and confectionary in general). Recently it has been also proposed as a gluten free food for celiac patients. After the first report of lupine anaphylaxis in 1994 [1], the prevalence of allergy to lupine (often as hidden food allergen) has increased [2,3]. We describe herein one case of severe anaphylaxis due to lupine in a young celiac patient.

A 23-year-old woman was referred to our unit after an episode of well documented anaphylaxis that occurred about 1 hour after eating a serving of gluten-free pasta with tomato sauce. The episode was characterized by generalized urticaria, upper airways angioedema, wheezing, laryngeal edema, vomiting, profound hypotension and loss of consciousness. She was promptly treated in an emergency care unit, with intramuscular epinephrine, intravenous antihistamines and steroids.

The patient had been recently diagnosed as having celiac disease, on the basis of positive family history, serological assays and jejunal biopsies. On the other hand, her clinical history was negative for allergic asthma and/or rhinitis, and skin prick tests for the common aeroallergens (mites, grasses, trees, molds, animal dander) proved, in fact, negative. Also skin tests and a CAP-RAST assay with a standard panel of food allergens (milk, egg, tomato, codfish, common fruits and vegetables) gave negative results, except for peanuts that proved mildly positive in the CAP-RAST assay (2.1 IU/mL, cutoff 0.35). In addition, she denied the consumption of unusual or special foods prior to the episode of anaphylaxis.

In agreement with the primary care physician, a provisional diagnosis of peanut allergy was made, based on the mild serum positivity and considering the possible presence of peanuts in foods as a hidden allergen, even though the patient denied any symptoms resulting from peanuts. At subsequent visits, after extensive questioning, the patient was able to provide the wrapping of the pasta she had eaten before the anaphylactic shock. We noticed among the ingredients the presence of lupine flour. The patient agreed that this was the only possibly new and unusual food. The suspected lupine allergy was then confirmed by the detection of specific immunoglobulin (Ig) E to lupine (>100 IU/mL, normal value <0.35 IU/mL) using the UniCAP test (Pharmacia Diagnostics, Uppsala, Sweden). A prick by prick test performed with fresh lupine also produced a strong positive reaction (9 × 3 mm wheal). In contrast, a prick-to-prick test with peanut also proved positive (5 × 3 mm wheal) but to a lesser extent. At this point we verified that the patient could eat peanuts. In fact she ate under our supervision 2 servings of peanuts (about 50 g) without problems, so that a challenge for peanuts was not needed. In addition, due to the severity of the previous reaction to lupine, we decided not to perform an oral blind challenge with this food.

This clinical case suggests some considerations. First, although cross-reactions between peanuts and lupines have been described [4], in this case a primary sensitization should be considered. We could not perform immunological assays, but we are confident that a cross-reaction was not relevant in this case, as the patient fully tolerated peanuts. Second, given the reported increasing allergy to lupine, the risk of sensitization to this food should be carefully monitored. This is particularly true as lupine is used as substitute for wheat flour, as is the case with celiac patients. Finally, in cases of "idiopathic" anaphylaxis the presence of this hidden allergen should be definitively ruled out.

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Erythema Multiforme to Tetrazepam

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Key words: Benzodiazepines. Drug-related skin allergy. Erythema multiforme. Patch test. Tetrazepam.

Palabras clave: Benzodiazepinas. Alergia cutánea a fármacos. Eritema exudativo multiforme. Test epicutáneos. Tetrazepam.

Erythema multiforme (EM) is a recurring inflammatory disease of the skin and mucus membranes that is often caused by such drugs as sulfamides, nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics, acetylsalicylic acid (ASA), antibiotics, and allopurinol [1,2]. Benzodiazepines can cause skin reactions but are seldom implicated in EM; tetrazepam has rarely been implicated [1,2]. A type IV hypersensitivity mechanism could explain a skin reaction several days after drug intake and positive patch tests have been reported [2-10]. An acute skin eruption is often preceded by fever and discomfort and accompanied by leukopenia, anemia (with normal mean cellular volume and mean corpuscular hemoglobin), blood in urine, and abnormal liver function [1,2]. We describe a 57-year-old woman who developed EM after tetrazepam administration. Patch tests were positive.

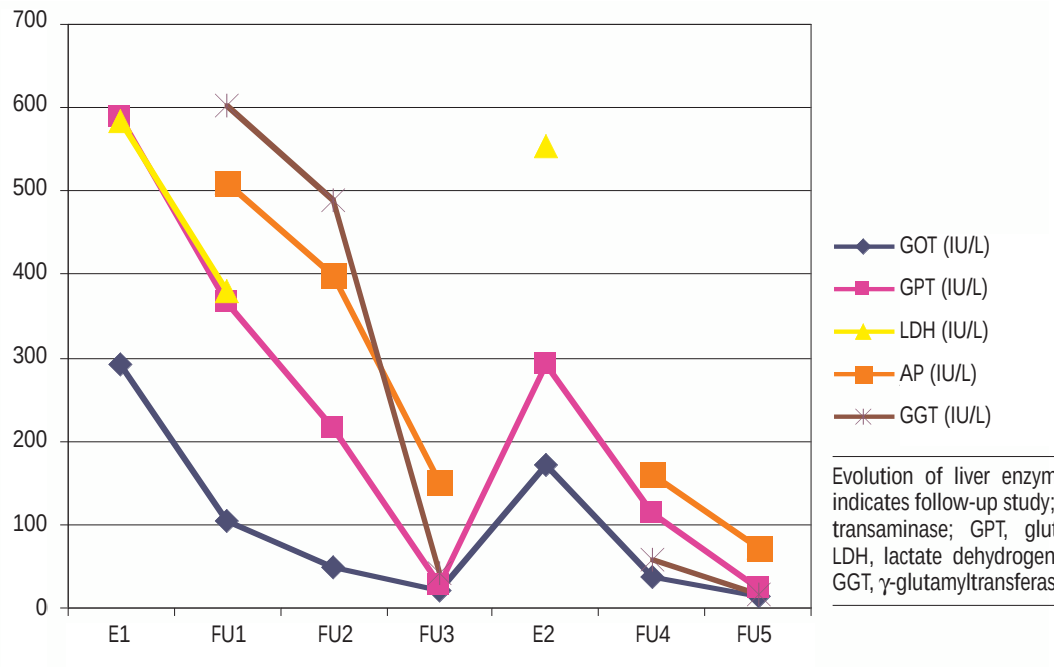
The patient developed an erythematous eruption similar to burns after several days' treatment with NSAIDs and tetrazepam. She expressed discomfort, experienced nausea, and went to an emergency room, where she received corticosteroids and antihistamines. Elevated liver enzymes were detected (figure).

Seven months later a similar eruption developed after intake of paracetamol and tetrazepam; again she suffered nausea, fever, and joint and muscle pain. Urine was dark. In an emergency room she received corticosteroids. Elevated liver enzymes (figure) and white blood cell counts (2970×10^9/L; 15.5% lymphocytes; 2.17% polymorphonuclear leukocytes) were detected. After this new episode the patient was referred to us. Following these episodes she tolerated metamizol, diclofenac, and ASA. She did not take benzodiazepines or paracetamol again. Blood was extracted for a hemogram and assessment of erythrocyte sedimentation rate, biochemistry, immunoglobulin (Ig) E, antinuclear antibodies (C3, C4), and proteins in blood. Complete urinalysis was performed. Glucose levels at the third and fifth follow-up visits and after the second episode were within normal limits (range, 112-132 mg/dL); bilirubin was also normal at the third, fourth, and fifth follow-up visits (range, 0.3-0.4 mg/dL). Other parameters were also normal. Prick tests with tetrazepam and paracetamol were negative; patch tests were positive to tetrazepam and negative to paracetamol at both 48 and 96 hours. Oral challenges with paracetamol until a cumulative therapeutic dose was reached caused no reaction. No oral challenge with benzodiazepines was performed because of reaction severity. The whole benzodiazepine group was forbidden.

Benzodiazepines, a group of drugs whose nucleus is a benzodiazepine ring, are used as anesthetics, sedatives, anticonvulsants, and for muscular spasms. The most common adverse reactions are psychomotor impairment, altered cognitive function, and paradoxical psychological effects. Tolerance and dependency can appear with prolonged use and cardiovascular and respiratory disorders may develop. Type I allergic reactions are infrequent. Reactions to tetrazepam include leukocytoclastic vasculitis, phototoxic reactions, generalized eruptions, fixed drug reactions, photo-onycholysis, contact dermatitis, EM-like eruptions, Stevens–Johnson syndrome, and toxic epidermal necrolysis [2-14]. Patch tests with 1% and 5% tetrazepam in petroleum jelly or in water were useful for diagnosis in all reports.

No study has shown cross-reactivity between tetrazepam and other benzodiazepines in spite of chemical similarity, especially with diazepam. The only difference between these drugs is the presence of a 5-phenyl ring in diazepam and 1-cyclohexen-1-yl in tetrazepam, and this structure can usually explain sensitization [1-3,7,9,10].

Our patient's first episode of EM developed after several days taking tetrazepam whereas only 3 doses triggered the second reaction. A negative oral challenge ruled out paracetamol as the culprit in the second reaction, but oral challenge with benzodiazepines was considered inadvisable.



Evolution of liver enzymes. E indicates episode; FU indicates follow-up study; GOT, glutamate oxaloacetate transaminase; GPT, glutamic-pyruvic transaminase,; LDH, lactate dehydrogenase; AP, alkaline phosphate; GGT, γ-glutamyltransferase.

Patch tests are not only useful in the case of orally induced tetrazepam allergy but also if contact allergy is suspected, so that oral challenge can be avoided.

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